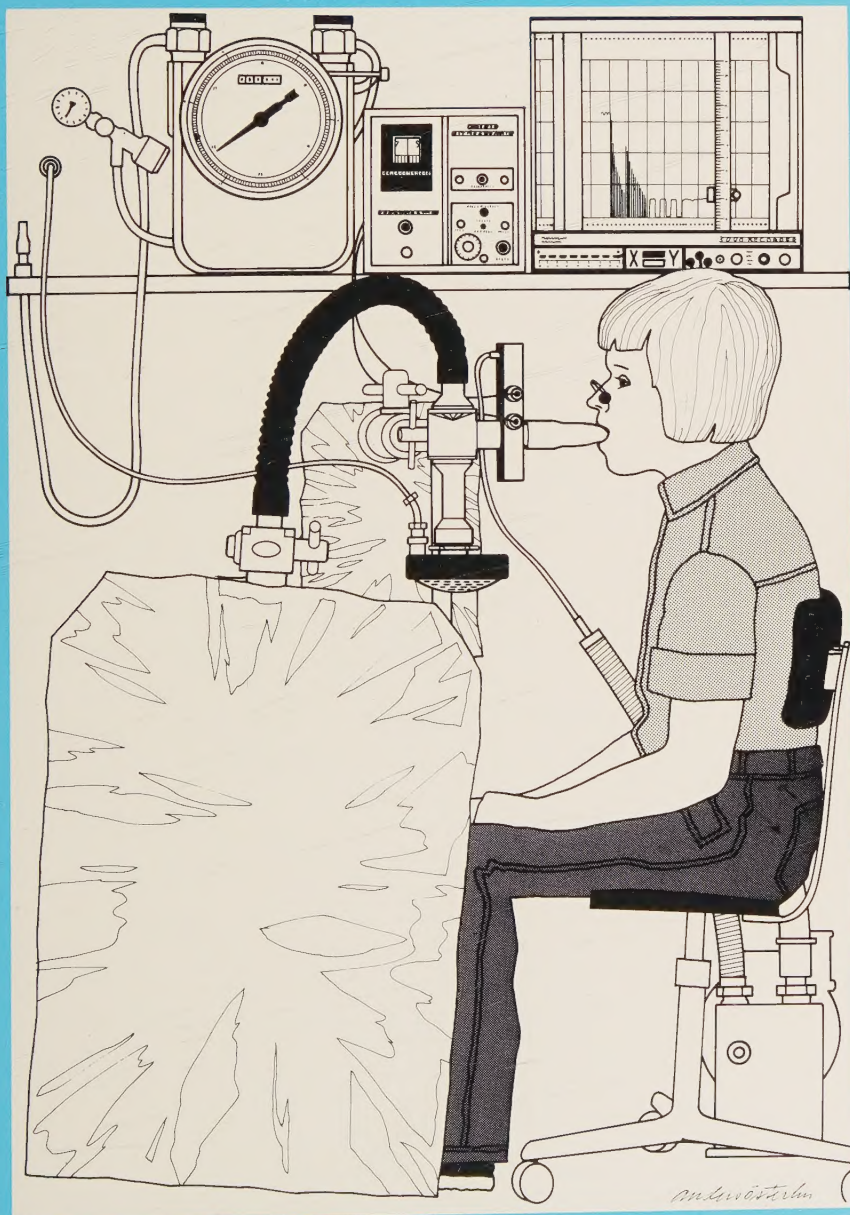


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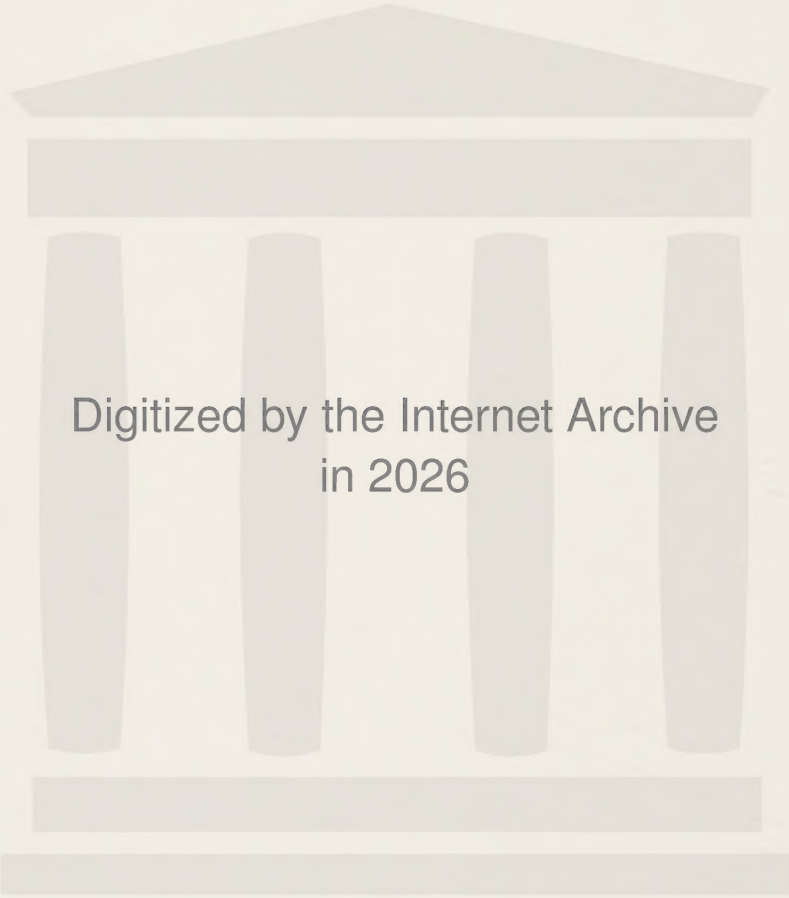
AVSTÄNGDA LUNGVOLYMER (VTG) HOS BARN

Förändringar vid obstruktiv lungsjukdom framför
allt ansträngningsutlöst astma (EIA)

EIVOR SVENONIUS



MALMÖ 1982



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Klinisk Fysiologi, Lunds Universitet, Allmänna Sjukhuset,
Malmö

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Förändringar vid obstruktiv lungsjukdom framför allt
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Konstnär Anders Österlin ritade omslagsbilden.

Denna studie har möjliggjorts genom ekonomiskt stöd från Svenska Nationalföreningen mot Hjärt- och Lungsjukdomar samt från Glaxo AB. Jag har för detta arbete även erhållit stipendium från Försäkringsbolaget Förenade Liv och från Svenska Nationalföreningen mot Hjärt- och Lungsjukdomar.



Till
mina bästa vänner,
mina barn,
Per, Maria och Erik

Denna avhandling utgör en sammanfattning av följande uppsatser:

- I. The volume of trapped gas in healthy children aged 7-16.
Lung 156: 71-77, 1979.
Tillsammans med R. Kautto.
- II. Flow volume measurements with a spirometer. Results from healthy children.
Lung 157: 201-208, 1980.
Tillsammans med R. Kautto och M. Arborelius Jr.
- III. Volume of trapped gas and maximum flow at 25% of vital capacity in exercise-induced asthma. I: "Small Airways in Health and Disease", under redaktion av P. Sadoul, J. Milic-Emili, B.G. Simonsson och T.J.H. Clark.
Excerpta Medica, sid. 21-26, 1979.
Tillsammans med M. Arborelius Jr och R. Kautto.
- IV. Lung function studies in children with allergic rhinitis.
Accepterad för publicering i Allergy.
Tillsammans med M. Arborelius Jr, R. Kautto och B. Lilja.
- V. Lung function in cystic fibrosis. Acute effect of salbutamol.
Respiration 40: 226-232, 1980.
Tillsammans med M. Arborelius Jr, R. Kautto, R. Kornfält och T. Lindberg.
- VI. Improvement after training of children with exercise-induced asthma.
Accepterad för publicering i Acta Paediatrica Scandinavica.
Tillsammans med R. Kautto och M. Arborelius Jr.

I den följande presentationen sker hänvisning till dessa uppsatser med deras romerska siffror.

INNEHÅLLSFÖRTECKNING

INLEDNING	7
METODER	9
FÖRSÖKSPERSONER	12
UPPSATS I: The volume of trapped gas in healthy children.....	15
UPPSATS II: Flow volume measurements with a spirometer.	
Results from healthy children.....	17
UPPSATS III: Volume of trapped gas and maximum flow at 25%	
of vital capacity in exercise-induced asthma.....	19
UPPSATS IV: Lung function studies in children with allergic	
rhinitis.....	21
UPPSATS V: Lung function in cystic fibrosis. Acute effect of	
salbutamol.....	23
UPPSATS VI: Improvement after training of children with	
exercise-induced asthma.....	25
ALLMÄN DISKUSSION.....	27
SLUTSATSER.....	29
SAMMANFATTNING PÅ ENGELSKA.....	30
TACK.....	31
LITTERATUR.....	32
Uppsatser I-VI.....	36

INLEDNING

Lungsjukdomar med obstruktivt inslag är vanliga hos barn (1, 26, 28) och utgör både diagnostiska och terapeutiska problem. Till de obstruktiva lungsjukdomarna räknas bronkialastma (1, 39). Frekvensen hos 7-åringar har noterats till 2.7% i ett svenskt material (26), och till 4-7% i åldrarna 6-18 år i ett amerikanskt material (39). Astmasjukdomen svarar för en tredjedel av de kroniska sjukdomarna i barnåren (39). Asthma bronchiale är ett betydande handikapp för det sjuka barnet och ger anledning till stor skolfrånvaro och frekventa sjukhusbesök. Vid andra allergiska sjukdomar som t.ex. hösnuva har somliga författare ansett att ett bronkospastiskt inslag föreligger (14, 15). Cystisk fibros anses också ha ett inslag av obstruktion i sin sjukdomsbild (41).

Vanlig spirometri, lungmekaniska undersökningar och blodgasanalyser har alla en viss sensitivitet för att påvisa astma men kan vara svåra att genomföra på barn, då undersökningarna fordrar god medverkan. På senare år har man blivit alltmer medveten om begränsningen hos konventionell spirometri när det gäller att påvisa förändringar i de fina luftvägarna (30). Forcerade andningsmanövrar är dessutom olämpliga, eftersom de kan utlösa bronkospasm hos barn med t.ex. astma (Fig. 3, uppsats I). Mätning av volymen avstängd gas (volume of trapped gas), VTG, i lungorna, enligt en metod som utvecklats i Malmö, har visat sig vara en känslig och specifik variabel för att påvisa abnormitet vid astma (11) och vid andra lungsjukdomar hos vuxna (27). Preliminära försök på barn med ansträngningsutlöst astma (exercise-induced asthma = EIA) visade att metoden var lätt tillämplig och tycktes ha hög sensitivitet (36).

Syftet med undersökningarna var:

*att modifiera VTG-metoden för användning på ett pediatriiskt material;
att jämföra dess känslighet för att påvisa tidig obstruktiv lungsjukdom med metoder som tidigare angivits som känsliga;
att pröva dess användbarhet i olika kliniska material, och
att följa dess förändringar i astmasjukdomen under terapi med fysisk träning enligt en ny modell.*

I. Eftersom VTG ej använts tidigare på barn, var det nödvändigt att modifiera metodiken och göra en studie av VTG på friska barn, så att referensvärden fanns inför tillämpningen på sjuka barn. VTG-fynden borde också relateras till gängse spirometrivariabler.

II. På senare år har man blivit alltmer medveten om begränsningen i konventionell spirometri när det gäller att påvisa förändringar i de fina luftvägarna. $V'_{\max 25}$ har lanserats som ett bra sätt att mäta funktionen i fina luftvägar (9, 35). Tekniken, som tidigare beskrivits, kräver komplicerad och dyrbar apparatur (10, 37, 38). Det syntes därför angeläget att göra en studie av möjligheten att mäta $V'_{\max 25}$ från FEV-kurvan mätt med vanlig spirometer.

III. Jämförelse mellan de två metoderna, VTG och $V'_{\max 25}$, hos friska barn respektive barn med astma typ EIA utfördes för att bedöma vilken av metoderna som var känsligast.

IV. Många författare anser att patienter med annan allergisk sjukdom som t.ex. hösnuva har ett bronkospastiskt inslag i sina luftvägar under sin besvärs-säsong eller i anslutning till fysisk ansträngning (14, 15, 17). Eftersom VTG är en känslig metod för att påvisa förändringar i luftvägarna, undersöktes barn med kliniskt säker hösnuva när de hade symptom och efter arbetsbelastning när de var helt symptomfria.

V. Vid cystisk fibros (CF) föreligger segt sekret i luftvägarna och eventuellt också bronkospasm som ger "air trapping", ojämn ventilation och minskad ventilationsförmåga. Patienter med sjukdomen undersöktes för att närmare kartlägga lungförändringarnas utveckling, utbredning och lokalisation till fina respektive grova luftvägar.

VI. Eftersom VTG visade sig känslig och reproducerbar för att påvisa EIA hos barn, undersöktes barn med denna sjukdom före och efter fysisk träning för att studera om EIA kunde påverkas av denna. En grupp barn med oförändrad livsföring tjänade som kontroll.

METODER

1. Lungfunktionsundersökningar

FRC: Funktionell residualkapacitet mättes med en kvävgasutsköljningsmetod (8). Försökspersonen inandades ren O_2 . N_2 -halten i utandningsluften följdes med Ohio 700 nitrogen analyser (Ohio, Houston, Texas) tills utandningsluften innehöll 2% N_2 .

VTG: När försökspersonens utandningsluft innehöll 2% N_2 , gjorde denne en maximal inhalation, en ventil slogs om och utandningsluften uppsamlades i en säck och denna luftblandning återandades med fem maximala andetag. N_2 -koncentrationen i återandningssäcken uppmättes. Den kvävgas som mobiliserades, definierades som "volume of trapped gas", efter omräkning till luftvolym i ml.

$$VTG = \frac{TLC \times FN_{2ER} - FRC \times 0.02}{0.80}$$

FN_{2ER} : N_2 -fraktionen vid slutet av återandningsperioden.

TLC: Totala lungkapaciteten.

WOV: Den utandade gasmängden (wash out volume) och

LCI: Lung clearance index ($LCI = WOV/FRC$) räknas ut från kvävgasutsköljningen (uppsats I).

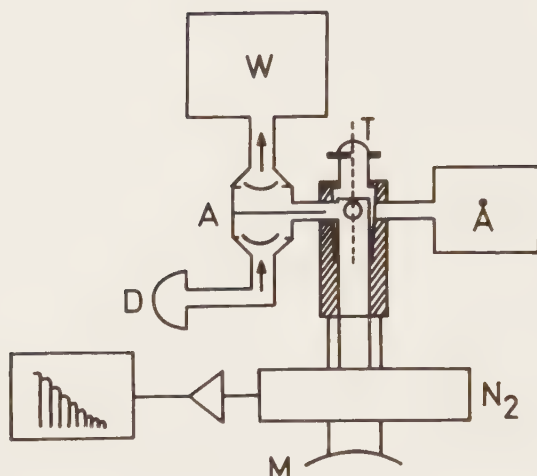


Fig. 1. Apparatur för VTG-mätning. Se f.ö. omslagsbilden!

M = munstycke;	A = andningsventil;
O = Demand-ventil;	W. = wash-out säck;
T = trevägskran;	Å = återandningssäck.

VC: Vitalkapaciteten och

FEV₁: den forcerade expiratoriska volymen på en sekund mättes med en spirometer (AB Kifa, Stockholm) av Bernstein-typ.

V' max 25: Maximala flödet vid 25% av VC uträknat från FEV-kurvan (uppsats II) (spirometers kymografhastighet 500 mm/sek; volymkalibrering 1 mm = 50 ml) genom att subtrahera 75% av FEV från överkanten på FEV-kurvan och derivering av genomsnittsflödet vid den höjden ± 0.1 sekund (5 mm) med hjälp av en tunn linje genom två punkter markerade på kurvan med en vass pennspets. Flödevolym kurvor mättes med pneumotachograf (Fleisch No. 3; Integrator = Siregnost FD91, Siemens-Elema AS, Erlangen, Väst-Tyskland), registrerades på X-Y-oscilloskop (Tectronix 603) och fotograferades med polaroidkamera (Polaroid CR 9 Land Camera).

Alla volymer omräknades till 37°C, rådande barometertryck, 100% luftfuktighet (BTPS). Samma laboratorieassistent assisterade vid samtliga studier.

2. Provokation av EIA

EIA provocerades genom löpning på rullande matta (Treadmill Standard Electric P2000-AE Baintree, 02184 Mass., U.S.A.) under 6 minuter i 5% uppförslutning. Hastigheten korrigerades uppåt eller neråt så att barnen inom de första 2 minuterna nådde pulsfrekvens 170 per minut. Hastigheten var i samtliga fall mellan 5 och 8 km per timme. EKG registrerades en gång per minut och användes för beräkning av pulsfrekvensen. Lungfunktionsprov gjordes före och 3-5 minuter efter avslutat arbete. Andningsfrekvensen räknades under 30 sekunder vid högsta belastningen. Arbetsprovokation efter träning gjordes med samma belastning som före.

3. Ergometri

Arbetsförmågan bedömdes genom belastning på en cykelergometer (typ AM 368; Elema-Schölander AB, Stockholm). Eftersom även otränade barn i allmänhet har en prestationsförmåga på cirka 2 W/kg kroppsvikt vid puls 170 och vi önskade minst tre belastningar, bestämdes utgångsbelastningen till 0.7 W/kg och ökningen var fjärde minut till 0.7 W/kg kroppsvikt, så att barnen på slutbelastningen arbetade vid en puls nära 170 per minut. EKG registrerades en gång per minut. Efter träningsperioden gjordes förnyad bedömning av arbetsförmågan vid puls 170/min.

4. Träningsprogram

Under överinseende av sjukgymnast premedicerades barnen med salbutamol i aerosol 0.2 mg respektive 20 mg natriumkromoglikat (DSCG). Därefter startade man med ett lätt uppvärmningsprogram under cirka 5 minuter, följt av två-minuterspass med löpning, hopprepshopp, jämfotahopp och "sit ups" med en belastning som inom en minut gav barnen en pulsfrekvens på minst 170 per minut. Detta upprepades med tvåminuterspauser i 30 minuter inräknat en enstaka längre paus på cirka 5 minuter. Mellan träningspassen hade man avslappning och andningsövningar. Resterande 25-30 minuter fick barnen simma eller leka i bassäng med 30° vatten. Bröstsimm eller crawl utfördes efter förmåga i perioder på minst 2 minuter. Denna del av träningen blev lekbetonad och populär.

5. Statistiska metoder

Student's t-test (34) användes både för parade observationer och jämförelse mellan grupper. Regressionsanalys gjordes enligt Snedecor (34). Metodfel (e = error of a single determination) beräknades enligt Dahlberg (13).

FÖRSÖKSPERSONER

Uppsats I

Efter samtycke från föräldrar och barn deltog 50 friska barn (22 pojkar och 28 flickor, 7-16 år gamla), fem barn i varje åldersgrupp, i lungfunktionsundersökningar inkluderande VTG, redovisade i uppsats I. Enligt skolhälsokorten var barnen friska och de hade aldrig haft någon allergisk sjukdom, ej heller hjärt-lungsjukdom och deras syskon och föräldrar hade inte astma. Ingen var rökare och ingen hade någon övre luftvägsinfektion vid undersökningstillfället.

Uppsats II

Dessa 50 friska barns spirometerkurvor användes också för att räkna fram V'_{max} 25.

Uppsats III

Efter samtycke från föräldrar och 10 friska barn, 9-16 år gamla, utfördes lungfunktionsundersökning och belastning genom löpning på rullande matta. Därefter gavs 0.2 mg salbutamol i aerosol. Förändringar i VTG hos dessa friska barn jämfördes med förändringar hos 16 astmasjuka barn (10 pojkar och 6 flickor, 9-16 år gamla). Dessa 16 astmabarn hade kliniskt säker astmasjukdom och gav en sjukhistoria med EIA.

Uppsats IV

Trettio polikliniska patienter, 8-17 år gamla, med svår hösnuva men utan anamnestiska och kliniska tecken på lungengagemang deltog efter eget och föräldrarnas samtycke i lungfunktionsundersökning inklusive VTG, dels då de var besvärsfria, dels under pollenssång. Sexton av dessa barn utförde också en

arbetsbelastning genom löpning på rullande matta under pollenfri säsong. Arbetsbelastning under pollenssäsong bedömdes efter försök ej genomförbar på grund av barnens uttalade allergiska ögon- och näsbesvär.

Uppsats V

Tolv barn med cystisk fibros (7 pojkar och 5 flickor), 6-18 år gamla, undersöktes beträffande lungfunktion inkluderande VTG före och efter inhalation av 0.2 mg salbutamol.

Uppsats VI

Femtio barn med kliniskt och lungfunktionsmässigt verifierad ansträngningsutlöst astma, 8-17 år gamla, undersöktes dels i vila, dels beträffande lungfunktion före och efter arbetsbelastning på rullande matta. Graden av EIA bedömdes härigenom.

Barnen var symptomfria och ej medicinerade under minst 12 timmar och DSCG var utsatt minst en vecka före undersökningen på laboratoriet. Minst 24 ml stegring i VTG, d.v.s. fyra gånger metodfelet (uppsats I) efter arbete krävdes för att diagnosen EIA skulle accepteras.

Barnens arbetsförmåga i W/kg kroppsvikt vid puls 170/min fastställdes. Därefter fick barnen efter eget val deltaga i tre olika träningsgrupper eller ej träna. Tre till fyra månader senare utförde barnen ånyo en lungfunktionsundersökning och kontroll av EIA och arbetsförmåga gjordes. Vid detta undersökningstillfälle utsattes DSCG och annan behandling minst 12 timmar före undersökningen i laboratoriet.

UPPSATS I

The volume of trapped gas in healthy children

Resultat och diskussion

Avstängda gasvolymen (VTG) mättes på 50 friska barn med tidigare beskriven metodik. VTG var linjärt korrelerad till kroppslängd och total lungkapacitet (TLC) och utgjorde hos de minsta barnen i medeltal 50 ml samt ökade hos de längsta till 80 ml. Hos alla barn, utom en pojke 180 cm lång, understeg VTG 100 ml.

Någon signifikant skillnad mellan pojkar och flickor kunde ej påvisas om hänsyn togs till kroppslängden. VTG utgjorde i ml = $TLC \text{ (i ml)} \times 0.011 + 30.79$ i hela materialet ($r = 0.75$; $RSD = 9.7 \text{ ml}$). $VTG \text{ (i ml)} = VC \text{ (i l)} \times 12.34 + 33.68$ ($r = 0.69$; $RSD = 10.7 \text{ ml}$). Dubbelbestämningar på 16 barn gav ett metodfel på 6.0 ml, d.v.s. förändringar $> 12 \text{ ml}$ är troligen ej slumpmässiga. Relationen VTG/TLC% i förhållande till ålder sjönk hos barn från 7-16 år, medan man hos vuxna såg ett med åldern stigande värde (Fig. 2) (12).

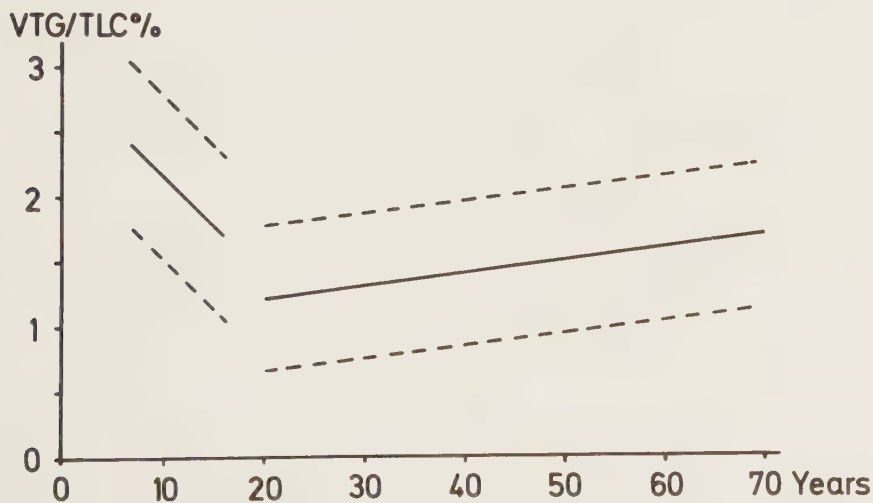


Fig. 2. Relationen VTG/TLC% i förhållande till åldern hos friska individer.

VTG är definitionsmässigt den kvävgasvolym som kan mobiliseras med återandning av VC fem gånger sedan kvävgaskoncentrationen i lungorna sjunkit till 2% under kvävgasutsköljning med syrgas.

VTG innehåller alltid en del kvävgas som frigörs från kroppsvävnaderna via blodet. Denna N₂-volym kan uppskattas till 20 ml hos vuxna, uttryckt som luft, motsvarande 25 ml av VTG (12). Eftersom denna N₂-volym är direkt korrelerad till kroppsstorlek och det är omöjligt att skilja extremt långsamt mobiliserade delar av FRC från kroppskvävet (12), har vi accepterat detta kroppskväve som en del av VTG. De faktorer som teoretiskt kan påverka VTG är bronkospasm, ödem och sekret samt en ökad lungeftergivlighet som vid emfysem. De första faktorerna ökar volymen ej ventilerade alveoler vid normala andetag. Dessa kan mobiliseras av det maximala transpulmonella trycket vid vitalkapacitetsandning. Föreligger emfysem eller andra tillstånd med lågt transpulmonellt tryck, kan eventuellt inte ens en maximal inandning öppna avstängda lungområden, varför VTG kan underskattas.

Teoretiskt sett kan avstängda lungområden helt eller delvis upptäckas med kroppsplethysmograf (7). Variabiliteten i kroppsplethysmograf-undersökningen (cirka ± 150 ml) är dock så stor att direkt jämförelse med VTG-metoden ej blir meningsfull. Delvis kan avstängda lungområden, som ej mobiliseras med maximala andetag före bronkdilatation, tänkas göra det sedan man med medikamenter minskat bronktonus, eftersom lägre transpulmonellt tryck då erfordras för att öppna förträngda luftrör.

Det är praktiskt lätt att mäta VTG ner till 6-7 års ålder. Den långsamma återandningen av tempererad, anfuktad luft utlöser ej bronkospasm, vilket FEV₁ och liknande prov kan göra hos patienter med EIA. VTG-metoden är billig att sätta upp.

UPPSATS II

Flow volume measurements with a spirometer. Results from healthy children

Resultat och diskussion

Flöde-volym kurvor, speciellt flödet vid 50% eller 25% av VC anses vara känsliga tester för att mäta tillståndet i de fina luftvägarna (9). Relativt komplicerad och dyr apparatur som kräver ofta upprepade kalibreringar har använts för att registrera flöde-volym kurvor (10, 37, 38).

Vanligen används en pneumotachograf (42) tillsammans med snabb X-Y-registrering på ett oscilloskop. Fotografisk registrering från oscilloskopet har i allmänhet använts. Pneumotachografen mäter som bekant flöde och volymen integreras från flödet. Även flöde-volym kurvan är en registrering av en maximal, snabb utandning, en FEV-manöver, där tidsaxeln utesluts och flödet plottats mot utandad volym. Kurvan kan rent logiskt ej innehålla någon information som ej finns i den vanliga FEV-kurvan (volym och tid), registrerad med god apparatur, som ej inför artefakter. Vid varje punkt på kurvan bör flödet kunna mätas genom derivering av volymförändringen. I detta arbete har vi testat denna hypotes praktiskt. Deriveringen har skett genom att en punkt 25% från baslinjen på den forcerade vitalkapaciteten har uppmätts. Från denna punkt har ± 0.1 sekund markerats på kurvan med en fin pennspets och en linje dragits genom dessa punkter.

Volymförändringen i denna deriverade linje motsvarande tiden en sekund har uppmätts och utgör $V'_{\max} 25$ (Fig. 1 i II). Samma utblåsning har mätts simultant med pneumotachograf med integrerad volym, vilken registrerats på oscilloskop. Kalibrering har skett enligt rekommendationer från tillverkaren av pneumotachografen.

Modellförsök: Identiska FEV-förlopp åstadkomna genom att gas som komprimerats i en behållare med 25 l volym fått strömma ut mot samma resistens jämfördes i andra försök. $V'_{\max} 25$ mätt med båda metoderna visade god korrelation ($r = 0.996$; $RSD = 0.09 \text{ l} \times \text{sek}^{-1}$).

Eventuella systematiska avvikelser kunde förklaras av ett systematiskt kalibreringsfel i pneumotachografen. Denna bör således kalibreras med kända flöden och volymer (10).

Det är således möjligt att beräkna flöden i den lägre delen av VC med en god spirometer. Mätningar av $V'_{max 25}$ med denna metod på FEV-kurvor, som registrerades i normalmaterialet (uppsats I), gav flödesvärden vid 25% av VC som överensstämde med dem av Zapletal et al. (42) givna med annan metodik. Vårt sätt att beräkna $V'_{max 25}$ är enklare, billigare och snabbare än från flödevolym kurvor erhållna med pneumotachograf och tillåter användning av FEV-kurvor i äldre material för $V'_{max 25}$ -beräkningar.

UPPSATS III

Volume of trapped gas and maximum flow at 25% of vital capacity in exercise-induced asthma

Resultat och diskussion

Ansträngningsutlöst astma har ansetts drabba såväl grova som fina luftvägar (36) och vissa författare anser att engagemang av fina luftvägar överväger (18, 29). VTG-proven hos våra barn med EIA tycks oftare vara patologiska än prov som avspeglar tillståndet i grova luftvägar (FEV_1), vilket kan tala för att fina luftvägar engageras tidigare (36). Det är också troligare att fina än grova luftvägar är avstängda vid normala andetag. EIA kan därför tjänstgöra som en modell för att jämföra känsligheten hos olika tester för sjukdom i fina luftvägar, i detta fall sannolikt bronkospasm. I detta arbete används samma material som i ett tidigare publicerat arbete (36) för beräkning av såväl VTG som $V'_{max} 25$. Den senare mättes enligt beskrivning i uppsats II. Övriga spirometriska och kvävgasutsköljningsvariabler fanns också tillgängliga. Materialet var kliniskt utvalt på så sätt att samtliga patienter anamnestiskt uppgav besvärande EIA.

Vid statistisk bearbetning fann man något mer signifikanta förändringar i VTG än i $V'_{max} 25$. Jämfört med utgångsvärdet minskade $V'_{max} 25$ efter ansträngning och ökade efter salbutamolinhalation ($P < 0.01$ respektive $P < 0.001$), medan VTG ökade signifikant efter arbete ($P < 0.001$) och efter salbutamol återgick till utgångsvärdet. Ser man på resultaten hos de enskilda individerna, så visade 93% av materialet, d.v.s. alla utom en försöksperson, en patologisk ökning av VTG efter ansträngning och en signifikant sänkning av VTG efter inhalation av salbutamol. Sextionio procent av materialet visade signifikant förbättring efter löpning 1 minut, vilket kan bero på en lätt sympaticusstimulering eller att det tidigare inhalede salbutamolet har verkat längre tid. Enbart hos 3 av de 16 astmabarnen (19%) sågs signifikant minskad $V'_{max} 25$ efter arbete, medan 63% av materialet visade signifikant förbättring efter salbutamol och 6% ytterligare förbättring efter en minuts löpning. Förändringen i $V'_{max} 25$ visade dock en dålig relation till förändringar i FEV_1 och det förefaller som FEV_1 , $V'_{max} 25$ och VTG delvis påverkas av förändringar på olika nivåer i luftvägarna. Om alla individer i det undersökta materialet antogs ha EIA efter arbete, är

alltså sensitiviteten för VTG-metoden betydligt högre än för V'max 25 metoden. Det kan påpekas att den enda individen som ej visade EIA med VTG-metoden ej heller hade sådan vid försöket, subjektivt, auskultatoriskt eller enligt FEV₁.

UPPSATS IV

Lung function studies in children with allergic rhinitis

Resultat och diskussion

Det har ofta framförts att en luftvägsallergi engagerar hela respirationsapparaten (14, 15, 17) även om vissa organ kan vara dominerande i den kliniska bilden. Barn med allergisk rinit skulle enligt denna hypotes alltid ha en varierande grad av bronkospasm, vilket ju kan ses som klinisk astma eller som ökad luftvägsirritabilitet.

Fyrtiotvå barn med hösnuva som sökte på Barnallergimottagningen på Malmö Allmänna Sjukhus, undersöktes och de barn som anamnestiskt och fysikaliskt hade tecken på astma (d.v.s. klinisk astma) sorterades bort. Resterande 30 barn undersöktes med spirometri plus kvävgasutsköljning, inkluderande VTG, dels när de hade uttalad hösnuva, dels under allergenfri säsong. Sexton av barnen provocerades dessutom med arbetsbelastning under symptomfritt intervall. Beskrivning av arbetsbelastningen finns i inledningen.

Samtliga barn blev undersökta kliniskt beträffande ögon, näsa, svalg, hjärta och lungor vid de olika undersökningstillfällena på Kliniskt Fysiologiska Avdelningen, Malmö Allmänna Sjukhus. Under pollenssäsongen sågs en obetydlig ökning av FRC och en minskning av LCI. De 16 barn, som utförde arbetstesten under pollenfri säsong, visade en lätt men signifikant ökning av VTG ($P < 0.05$) utan att denna blev abnormt stor, möjligen som uttryck för en subklinisk spasm i de fina luftvägarna. Inhalation av 0.2 mg salbutamol efter arbetsbelastning reducerade VTG ($P < 0.01$). V'_{max} 25/TLC minskade ej efter arbetsbelastning, men efter salbutamol sågs en signifikant ökning ($P < 0.05$) jämfört med ursprungsvärdena.

Barn med hösnuva hade sålunda en tendens till bronkospasm efter ansträngning under den pollenfria säsongen, men förändringen saknar klinisk betydelse, eftersom deras VTG också efter ansträngning låg inom normalvariationen och ingen hade kliniska symptom. Ingen av de 30 barnen med hösnuva har hittills (4

är efter undersökningen) utvecklat astma. Generellt engagemang av nedre luftvägar vid hösnuva tycks således ej vara vanligt hos barn, som ej har klinisk astma.

UPPSATS V

Lung function in cystic fibrosis. Acute effect of salbutamol.

Resultat och diskussion

Cystisk fibros (CF) är en ärftlig sjukdom av okänd genes. Den drabbar sannolikt generellt funktionen av både mukösa och serösa körtlar och ger kliniska besvär från framför allt gastrointestinalkanalen (pankreasinsufficiens) och andningsapparaten (obstruerande segt slem) med fibros och emfysem som följd (21, 33, 40, 41).

Olika lungfunktionstester har gjorts på barn med CF för att fastställa sjukdomens svårighetsgrad och utveckling (16, 41). Lungfunktionen hos barn med CF karakteriseras av förlust av elasticitet i lungan, luftvägsobstruktion som ger "air trapping", ojämn ventilation, minskad ventilationsförmåga och sekundär perfusionsrubbning (16, 41).

I detta arbete undersöktes lungfunktionen hos 12 barn med CF. Deras sjukdomsbild graderades enligt Shwachman och Kulczycki (33) enligt ett score-system från 0 till 100, där 100 innebär symptomfrihet. Lungfunktionsundersökningar gjordes före och 10 minuter efter inhalation av 0.2 mg salbutamol. De 12 barnens lungfunktion avvek signifikant från normala barns, såväl i fråga om funktionen i fina (VTG och $V'_{max} 25$) som grova luftvägar (FEV_1). VC låg inom normala gränser (se Tabell 2 i V).

Efter inhalation av 0.2 mg salbutamol sågs ingen signifikant förbättring i någon lungfunktionsvariabel. Små förbättringar, dock ej signifikanta, sågs i $FEV\%$, FEV_1 och $V'_{max} 25$. VTG visade till skillnad mot vad som vanligen ses vid astma, en mindre, dock ej signifikant, ökning. Efter inhalation av salbutamol från jet-nebulisationsapparat (våt aerosol) i kliniken rapporterade barnen subjektiv förbättring. Denna effekt kan hypotetiskt bero på bronkdilatation av samma typ som kan anas i denna undersökning, anfuktning med lösare sekret med förbättrad mukociliär transport som följd och/eller på placeboeffekt.

De flesta barn med CF har kliniskt sett abnorm lungfunktion. I detta material upptäcktes vid dynamisk spirometri (FEV_1 och $FEV\%$) abnormiteter i lungfunktionen endast hos 50% av barnen. Det nya provet, VTG, avslöjade abnormitet hos 11 av de 12. Näst bästa testen var LCI (9/12), medan $V'_{max} 25/TLC$ avslöjade abnormitet hos 8 av 12 patienter.

VTG tycks således vara en känslig metod för att upptäcka abnormitet även vid andra lungsjukdomar än astma. Inslaget av reversibel bronkospasm vid CF är tveksamt. Bronkobstruktion av annan genes och varierande grad av emfysem anses vanligt (16, 21). För hög VTG är alltså ej patognomoniskt för astma utan tycks ospecifikt vid obstruktion. Möjligen kan minskning av VTG efter bronkdilatation vara typiskt för reversibel bronkospasm.

UPPSATS VI

Improvement after training of children with exercise-induced asthma

Resultat och diskussion

Ansträngningsutlöst astma (5, 18, 22, 23, 24, 28, 29, 43) är ofta det största handikappet för barn med astma och förekommer hos dessa i upp till 90%. Barn har vanligen en hög aktivitetsnivå. Om de inte kan delta i fysiska aktiviteter som lek och idrott, blir de ofta isolerade från sina kamrater och överbeskyddade av de vuxna med tilltagande invaliditet som följd. Olika träningsprogram har prövats (4, 20, 31, 32) för att förbättra fysisk arbetsförmåga och basalastma hos astmabarn. Några större förbättringar har inte kunnat noteras, förmodligen på grund av att effektiv arbetsbelastning begränsas av barnens tendens att få EIA (20). Effektiv träning skulle hypotetiskt vara möjlig, om EIA kunde förhindras genom premedikation (6, 19) och om man valde en typ av arbete som gav god kardio-pulmonell träning utan att ge alltför mycket hyperventilation (25, 45).

Femtio barn med anamnes på EIA deltog i undersökningen. Grupp 1 bestod av 10 barn (4 flickor och 6 pojkar), 9-17 år gamla med oförändrad fysisk aktivitet. Grupp 2: Kontrollerad träning, premedikation med 0.2 mg salbutamol i aerosol. Gruppen bestod av 10 pojkar och 2 flickor, 9-16 år gamla. Grupp 3: Kontrollerad träning av 10 pojkar och 3 flickor i åldern 8-16 år. Behandling med DSCG 20 mg x 4, där en av doserna togs före träningen. Grupp 4 bestod av 15 barn (11 pojkar och 4 flickor, 9-16 år gamla), som tränade i egen regi, vanligtvis efter premedikation med inhälation av 0.2 mg salbutamol. Basal medikation, salbutamol och/eller theofyllin vid behov, ändrades ej för någon av grupperna.

Samtliga barn undersöktes med lungfunktionstester och graden av deras EIA uppmättes med arbetsprovokation på rullande matta. Barnens arbetsförmåga bedömdes i W/kg vid puls 170 per minut på cykelergometer. Lungfunktionen före och 5 minuter efter löpning på rullande matta uppmättes och förändringarna ansågs bero på EIA. Barnens arbetsförmåga i W/kg vid puls 170 och bedömningen av EIA utfördes före och efter träningsperioden.

Barnen, som deltog i den kontrollerade träningen, följde ett träningsprogram och de tränade en timme två gånger i veckan under 3-4 månader.

I de fyra grupperna förelåg ingen signifikant skillnad i lungfunktionsprov före träningen och inga signifikanta skillnader i arbetsförmågan mellan grupperna före träningsperioden med undantag av grupp 3, som hade en lägre initial arbetsförmåga än grupp 1 och 2. De 50 astmabarnens arbetsförmåga överensstämde väl med resultaten rapporterade av Adams et al., Graff-Lonnevig och Åstrand (2, 3, 20, 44).

Den ansträngningsutlösta astman minskade signifikant i alla tränande grupper, både mätt som FEV₁ (grova luftvägar) och som VTG (fina luftvägar), medan grupp 1 var oförändrad (Fig. 1 i VI). Arbetsförmågan ökade signifikant i grupp 2, medan grupp 3 och 4 visade liknande förbättring, som dock ej var signifikant. Grupp 1 visade ej signifikant försämring (Fig. 2 i VI).

Hos de tränande barnen noterades ett större välbefinnande såväl psykiskt som fysiskt och barnens frekvens av astmaattacker minskade. Samtliga barn deltog, ofta sporadiskt, i skolgymnastiken, men efter träningsperioden rapporterades de tränande barnen ha en bättre närvaro. Intresset för motion hade väckts och barnen hade lärt sig undvika sin ansträngningsutlösta astma genom premedikation och lämplig träningsteknik.

Barnen kunde deltaga i olika aktiviteter utan att hindras av sitt fysiska handikapp och flera av barnen tävlingsidrottar framgångsrikt (tennis, volleyboll, simning och fotboll). Fysisk träning efter premedicinering har alltså visat sig vara ett viktigt led i behandlingen av astmabarn.

ALLMÄN DISKUSSION

På senare år har man blivit alltmer medveten om begränsningarna av konventionell spirometri när det gäller att påvisa förändringar i de fina luftvägarna (30). Mätning av VTG är en känslig metod för att avslöja förändringar i fina luftvägar (11, 36) och tycks känsligare än andra metoder för att upptäcka bronkospasm (uppsats III). VTG är den mobiliserbara kvävgasvolymen efter N_2 -utsköljning, omräknad till luft. Den har tidigare endast använts i ett fåtal undersökningar på vuxna (11, 27) och aldrig på barn. Vid undersökning av 50 friska barn i åldern 7-16 år var VTG bäst korrelerad till TLC och VC. VTG/TLC% och VTG/VC% var de bästa variablerna för kliniskt bruk. Metodfelet för VTG var endast 6.0 ml. VTG/TLC% sjönk med åldern från 7 till 16 år, medan samma värde steg med stigande ålder från 20 år.

VTG-metoden är billig att sätta upp, enkel att utföra för både patient och personal och ger inte lika lätt upphov till bronkospasm som upprepade bestämningar av FEV_1 gör hos astmatiker.

Flöde-volym kurvor, speciellt flödet vid 50% och 25% av VC, är en känslig test för mätning av tillståndet i fina luftvägar (9). Komplicerad och dyrbar apparatur, som kräver upprepade kalibreringar, har tidigare använts (10, 38). Vid jämförelse med tidigare använda metoder med mätning direkt från den forcerade FEV-kurvan sågs en mycket god korrelation ($r = 0.996$) och värden från 50 friska barns FEV-kurvor stämde väl med dem av Zapletal et al. (42). Detta förenklade sätt att mäta V'_{max} 25 sparar tid och dyrbar, komplicerad apparatur (10, 37, 38).

Jämförelse mellan de två metoderna, VTG och V'_{max} 25, för att mäta tillståndet i fina luftvägar gjordes på 16 barn med EIA och 10 friska barn i matchande ålder. Båda metoderna var känsliga, men VTG var överlägsen V'_{max} 25 för att avslöja abnormitet hos den enskilde individen.

Hos 30 barn med allergisk rinit undersökta under pollen- respektive pollenfri säsong sågs inga tecken på bronkobstruktion under besvärssäsongen mätt med den känsliga VTG-metoden. Dessa fynd skiljer sig från tidigare publicerade undersökningar (14, 15, 18). Sexton av barnen uppvisade efter arbetsbelastning signifikant VTG-ökning och en signifikant VTG-minskning efter salbutamol så som

barn med EIA (36). Förändringarna saknar dock klinisk betydelse, eftersom VTG vid samtliga undersökningstillfällen låg inom normalvariationen och barnen ej hade kliniska symptom på bronkobstruktion.

CF-barns lungfunktion karakteriseras av förlust av elasticitet och luftvägsobstruktion, som ger "air trapping", ojämn ventilation, minskad ventilationsförmåga och sekundär perfusionsrubbnig. Elva av tolv CF-barn var abnorma i VTG, medan endast två av tolv och åtta av tolv hade abnorma värden i FEV₁ respektive V'max 25. Andra författare har konstaterat signifikant förbättring av FEV₁ efter inhalation av β_2 -agonist (16). I det aktuella materialet sågs ingen sådan förbättring och VTG ökade något.

Ansträngningsutlöst astma är vanligen det största handikappet hos barn med astma och förekommer i 90% av dem. Femtio barn med EIA uppdelades i fyra grupper, där grupp 1 var kontrollgrupp och övriga tre grupper tränande grupper (två grupper med kontrollerad träning och en grupp träning i egen regi). Träning skedde i tvåminuterspass efter premedicinering med salbutamol eller DSCG 1 timme 2 ggr/vecka under 3-4 månader. .

Den ansträngningsutlösta astman minskade signifikant i alla tränande grupper, mätt både som FEV₁ (grova luftvägar) och som VTG (fina luftvägar), medan kontrollgruppen förblev oförändrad. Arbetsförmågan (W/kg kroppsvikt vid puls 170) ökade signifikant ($P < 0.01$) i grupp 2 (kontrollerad träning och premedicinering med salbutamol). Övriga tränande grupper visade likartad ökning av prestationsförmågan, medan kontrollgruppen sjönk obetydligt.

De tränande barnen fick ökat intresse för motion och rapporterade större närvaro vid gymnastik- och idrottslektioner och lägre frekvens av astma-attacker. Sju av de tränande barnen deltar i tävlingsidrott (simning, cykling, volley-boll och fotboll).

Generellt förbättrar fysisk träning med här använd metod patienternas fysiska och psykiska välbefinnande mer än tidigare använd terapi (4, 20, 21, 32).

SLUTSATSER

1. VTG-mätning är en känslig metod för att avslöja obstruktion i fina luftvägar.
2. Flöde-volym kurvor som $V'_{max} 25$ kan uträknas direkt från spirometerkurvan, vilket förenklar arbetet för såväl patient som personal och sparar dyrbar och komplicerad utrustning.
3. VTG är känsligare än $V'_{max} 25$ för att mäta obstruktion i fina luftvägar hos barn med astma.
4. Barn med allergisk rinit har inte obstruktion i sina luftvägar under sin besvärssäsong (mätningar med konventionell spirometri och VTG), men efter arbetsbelastning ses tendens till bronkospasm (signifikant VTG-ökning efter arbetsbelastning, signifikant VTG-minskning efter salbutamolinhalation). VTG efter arbete når dock ej någon patologisk nivå och kliniskt noteras inga tecken på bronkospasm.
5. VTG är känsligare än andra tester för att urskilja lungförändringar hos barn med cystisk fibros. Elva av tolv barn med CF hade patologisk VTG, medan två respektive åtta av de tolv var abnorma i FEV₁ respektive $V'_{max} 25$. Salbutamolinhalation ger ingen signifikant förbättring i någon lungfunktionsvariabel hos barn med CF.
6. EIA minskar signifikant hos barn som träningsbehandlades efter premedicinering 2 ggr/vecka under 3-4 månader. Icke tränande barn är oförändrade. Barnens basala astma förbättras under träningsperioden.
7. Arbetsförmågan mätt i W/kg kroppsvikt vid puls 170/min ökar signifikant ($P < 0.01$) hos astmabarn som premedicineras med salbutamol och deltar i kontrollerad träning.
8. Fysisk träning efter premedicinering är ett viktigt led i behandlingen av astmabarn och förbättrar ofta deras tillstånd såväl fysiskt som psykiskt mer än någon tidigare använd terapi.

VOLUME OF TRAPPED GAS (VTG) IN CHILDREN
Changes in obstructive lung diseases, particularly in
exercise-induced asthma (EIA)

VTG is the volume of nitrogen mobilized by maximal breaths after N_2 wash out down to 2% expressed as air. Increased VTG reveals bronchospasm with high sensitivity. VTG in 50 healthy children was positively related to height and TLC and varied between 50 ml and 80 ml. The error of a single determination was 6.0 ml.

Maximum flow at 25% VC ($V'_{max} 25$) was calculated from spirometer curves. This method was compared with the conventional method using a pneumotachograph and an X-Y oscilloscope. A good correlation between the two methods was obtained ($r = 0.996$).

VTG was more accurate than $V'_{max} 25$ for evaluating exercise-induced bronchospasm.

VTG from 30 children with allergic rhinitis revealed no signs of bronchospasm in their pollen season. VTG increased significantly after 6 minutes' running during the pollen-free season and decreased significantly after salbutamol inhalation indicating a bronchospastic reaction, however, always within the normal range of VTG.

In children with cystic fibrosis (CF), VTG revealed abnormality in 11 out of 12, while the same figure for $V'_{max} 25$ /TLC was 8/12 and for $FEV_1/VC\%$ 6/12. No significant improvement was seen after salbutamol aerosol.

Forty children with EIA trained after premedication with salbutamol or disodium chromoglicate. EIA decreased and working capacity increased in training children but not in the ten controls.

VTG is superior to other methods for revealing early bronchospasm. Training according to our programme improves the children's physical and mental condition more than previous therapy.

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LITTERATUR

1. Aas, K.: Allergic asthma in childhood. Arch Dis Childh 44: 1-10, 1969.
2. Adams, F.H., Bengtsson, E., Berven, H. & Wegelius, C.: The physical working capacity of normal school children. II. Swedish city and country. Pediatrics 28: 243-257, 1961.
3. Adams, F.H., Linde, L.M. & Miyake, H.: The physical working capacity of normal school children. I. California. Pediatrics 28: 55-64, 1961.
4. American Academy of Pediatrics: Committee on Children with Handicaps: The asthmatic child and his participation in sports and physical education. Pediatrics 45: 150-151.
5. Anderson, S.D., Seale, J.P., Ferris, L., Schoeffel, R. & Lindsay, D.A.: An evaluation of pharmacotherapy for exercise-induced asthma. J Allergy 64: 612-624, 1979.
6. Anderson, S.D., Silverman, M., König, P. & Godfrey S.: Exercise-induced asthma. Br J Dis Chest 69: 1-38, 1975.
7. Bedell, G.N., Marshall, R., DuBois, A.B. & Comroe Jr, J.H.: Plethysmographic determination of the volume of gas trapped in the lungs. J Clin Invest 35: 664-670, 1956.
8. Bouhuys, A., Hagstam, K.E. & Lundin, G.: Efficiency of pulmonary ventilation during rest and light exercise. A study of alveolar nitrogen wash out curves in normal subjects. Acta Physiol Scand 35: 289-304, 1956.
9. Bouhuys, A., Hunt, V.R., Kim, B.M. & Zapletal, A.: Maximum expiratory flow rates in induced bronchoconstriction in man. J Clin Invest 48: 1159-1168, 1969.
10. Bouhuys, A. & Virgulto, J.A.: Calibration of flow-volume curves. Lung 155: 123-130, 1978.
11. Bülow, K., Arborelius Jr, M., Christensson, P. & Lilja, B.: Changes in volume of trapped gas in the lungs during provoked asthma followed by β_2 -receptor stimulation. Respiration 6: 19-27, 1978.
12. Christensson, P., Arborelius Jr, M. & Kautto, R.: Volume of trapped gas in lungs of healthy humans. J Appl Physiol 51: 172-175, 1981.
13. Dahlberg, G.: Statistical Methods for Medical and Biological Students, sid. 122-132. George Allen & Unwin Ltd., London, 1974.

14. Doggett, W.E., Chester, E.H., Belman, M.J. & Schwartz, H.J.: Prevalence of airway obstruction in allergic rhinitis. Am Rev Respir Dis 113: 158, 1976.
15. Fairshter, R.D., Novey, H.S., Marchioli, L.E. & Wilson, A.F.: Large airway constriction in allergic rhinitis: Response to inhalation of helium-oxygen. J Allergy Clin Immunol 63: 39-46, 1979.
16. Featherby, E.A., Weng, T.R., Crozier, D.N., Duic, A., Reilly, B.J. & Levison, H.: Dynamic and static lung volumes, blood gas tension and diffusing capacity in patients with cystic fibrosis. Am Rev Respir Dis 102: 737-749, 1970.
17. Godfrey, S.: Exercise Testing in Children. Applications in Health and Disease. W.B. Saunders Co. Ltd., London, 1974.
18. Godfrey, S.: Exercise-induced asthma. Allergy 33: 229-237, 1978.
19. Godfrey, S. & König, P.: Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children, Pediatrics 56: Suppl: 930-934, 1975.
20. Graff-Lonnevig, V.: Cardio-respiratory function, aerobic capacity and effect of physical activity in asthmatic boys. Akademisk avhandling, Karolinska Institutet, Stockholm, 1978.
21. Gurwitz, D., Corey, M., Francis, P.W.J., Crozier, D. & Levison, H.: Perspectives in cystic fibrosis. Pediatr Clin North Am 26: 603-615, 1979.
22. Hartley, J.P.R.: Exercise-induced asthma. Thorax 34: 571-574, 1979.
23. Inbar, O., Alvarez, D.X. & Lyons, H.A.: Exercise-induced asthma - a comparison between two modes of exercise stress. Eur J Respir Dis 62: 160-167, 1981.
24. Jones, R.S., Buston, M.H. & Wharton, M.J.: The effect of exercise on ventilatory function in the child with asthma. Br J Dis Chest 56: 78-86, 1962.
25. Kilbom, R.: Physical training in women. Scand J Clin Lab Invest Suppl 119, 1971.
26. Kjellman, N.I.M.: Immunglobulin E and atopic allergy in childhood. Akademisk avhandling. Linköping University Medical Dissertations No. 36, 1976.

27. Lilja, B., Arborelius Jr, M., Janzon, L., Länsimies, E. & Lindell, S.E.: The volume of trapped gas, closing volume and pulmonary gas exchange in smokers and non-smokers aged 60. Scand J Respir Dis Suppl 95: 48-59, 1976.
28. McFadden Jr, E.R.: An analysis of exercise as a stimulus for the production of airway obstruction. Lung 159: 3-11, 1981.
29. McFadden Jr, E.R., Ingram Jr, R.H., Haynes, R.L. & Wellman, J.J.: Predominant site of flow limitation and mechanisms of postexertional asthma. J App Physiol 42: 746-752, 1977.
30. Rodarte, J.R., Hyatt, R.E., Rehder, K. & Marsh, H.M.: New test for the detection of obstructive pulmonary disease. Chest 72: 762-768, 1977.
31. Scherr, M.S. & Frankel, L.: Physical conditioning program for asthmatic children. JAMA 168: 1996-2000, 1958.
32. Seligman, T., Randel, H.O. & Stevens, J.J.: Conditioning program for children with asthma. Phys Ther 50: 641-650, 1970.
33. Shwachman, H. & Kulczycki, L.: Long-term study of one hundred five patients with cystic fibrosis. J Dis Childh 96: 6-15, 1958.
34. Snedecor, G.W.: Statistical Methods, 5:te uppl, sid. 35-66 & 122-193, The Iowa State College Press, Iowa, 1956.
35. Souhrada, J.F. & Buckley, J.M.: Pulmonary function testing in asthmatic children. Pediatr Clin North Am 23: 249-277, 1976.
36. Svenonius, E., Lecerof, H., Lilja, B., Arborelius Jr, M. & Kautto, R.: The volume of trapped gas: A new and sensitive test for the detection of exercise-induced bronchospasm in children. Acta Paediatr Scand 67: 583-589, 1978.
37. Takishima, T., Sasaki, T., Takahashi, K., Sasaki, H. & Nakamura, T.: Direct-writing recorder of the flow-volume curve and its clinical application. Chest 61: 262-266, 1972.
38. Virgulto, J. & Bouhuys, A.: Electronic circuits for recording of maximum expiratory flow-volume (MEFV) curves. J Appl Physiol 35: 145-147, 1973.
39. Weiss, B. & Segal, M.S. (red.): Bronchial Asthma. Mechanisms and Therapeutics. Little, Brown and Company, Boston, 1976.

40. Wood, R.E., Wanner, A., Hirsch, J. & Farrekk, P.M.: Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. Am Rev Respir Dis 111: 733-738, 1975.
41. Zapletal, A., Motoyama, E.K., Gibson, L.E. & Bouhuys, A.: Pulmonary mechanics in asthma and cystic fibrosis. Pediatrics 48: 64-72, 1971.
42. Zapletal, A., Motoyama, E.K., van de Woestijne, K.P., Hunt, V.R. & Bouhuys, A.: Maximum expiratory flow-volume curves and airway conductance in children and adolescents. J Appl Physiol 26: 308-316, 1969.
43. Zeballos, R.J., Shturman-Ellstein, R., McNally Jr, J.F., Hirsch, J.E. & Souhrada, J.F.: The role of hyperventilation in exercise-induced bronchoconstriction. Am Rev Respir Dis 118: 877-884, 1978.
44. Åstrand, P.O.: Experimental Studies of Physical Working Capacity in Relation to Sex and Age. Akademisk avhandling, Stockholm. Munksgaard, Köpenhamn, 1952.
45. Åstrand, P.O. & Rodahl, K.: Textbook of Work Physiology. Kap. 19. McGraw-Hill Inc., New York, 1977.



The Volume of Trapped Gas in Healthy Children Aged 7 – 16

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Abstract. A new and sensitive lung function test, the volume of trapped gas (VTG), as well as conventional lung function tests were measured in 22 boys and 28 girls, aged 7 to 16, all healthy. The VTG was best correlated to total lung capacity (TLC) and also showed a good correlation to height (H), vital capacity (VC), wash out volume (WOV), and forced expiratory volume in one second (FEV₁). VTG/TLC% or VTG/VC% are probably the best variables for clinical use. The error of a single determination in VTG was only 6 ml, and in VTG/TLC% it was 0.16, giving a variance of about 10%. The reproducibility of VTG and VTG/TLC% must be regarded as good. The VTG test can be performed in children aged 5 and older.

Key words: Lung volume, child – Volume of trapped gas (VTG), normal values – Spirometry, normal values.

After provocation with allergens [5] or exercise [14], increases in the volume of trapped gas (VTG) reveal with high sensitivity both subclinical and manifest bronchospasm. Measurement of VTG is definitely superior to FEV₁, to other spirometric variables, and to the lung clearance index (LCI), but it has not been compared to other methods thought to be sensitive in the detection of slight degrees of asthma [4, 15]. In patients with asthma, the test might be suitable for diagnosing as well as monitoring the response to therapy, if reference values were available and the repeatability was known in healthy subjects. The present study presents reference values from healthy children in whom lung function was also defined by static and dynamic spirometry, including functional residual capacity measured with a multiple breath nitrogen washout technique.

Subjects and Methods

Abbreviations

VC = vital capacity
TLC = total lung capacity

- FRC = functional residual capacity
 RV = residual volume
 FEV₁ = forced expiratory volume in one second
 WOV = wash out volume = exhaled volume to reach 2% N₂ during oxygen breathing
 LCI = lung clearance index = WOV/FRC
 VTG = volume of trapped gas
 FN₂ER = N₂ fraction at the end of the rebreathing period. The method has been described in detail elsewhere [5, 11, 14].

Fifty children (22 boys, 28 girls) participated; informed consent was obtained from their parents. Their ages ranged from 7 to 16, and there were 5 children for each year group. According to school records, they were healthy, and their heights and weights were within $M \pm 2$ SD of Swedish children of the same age [9]. Their physical characteristics are given in Table 1. The children had never had any allergic, lung, or heart disease, and their parents, brothers, and sisters did not have asthma. No smokers or children with signs of respiratory infection at the time of examination were included.

Table 1. Physical characteristics of 50 healthy children

	Boys (n = 22)		Girls (n = 28)	
	Mean value	Range	Mean value	Range
Age	11.0 years	7 – 16	11.9 years	7 – 16
Height	148.1 cm	125 – 181	150.2 cm	122 – 171
Weight	37.5 kg	21 – 69	40.2 kg	

In order to analyze the error of a single determination [7], double determinations on the same day with an interval of 15 – 60 min were performed on 16 children aged 7 to 16 (9 boys, 7 girls).

A multiple breath nitrogen washout procedure was continued until the end-expiratory nitrogen concentration reached 2% [3]. The subject then inhaled maximally. A stopcock was turned, and he rebreathed with five vital-capacity breaths into an empty, oxygen-washed rebreathing bag. The nitrogen concentration usually reached a plateau after this maneuver, and the subject next exhaled maximally into the bag. The VTG was defined as the nitrogen thus mobilized, expressed as air [11]:

$$VTG = \frac{TLC \times FN_2ER - FRC \times 0.02}{0.80}$$

VTG was also expressed in percent of TLC and VC (VTG/TLC% and VTG/VC%). The nitrogen washout data were used for calculation of FRC, WOV, and LCI, all of which were corrected for nitrogen in the instrumental dead space (40 ml).

After these measurements, static and dynamic spirometry was performed in the sitting position with a Bernstein-type spirometer. Slow vital capacity and forced ma-

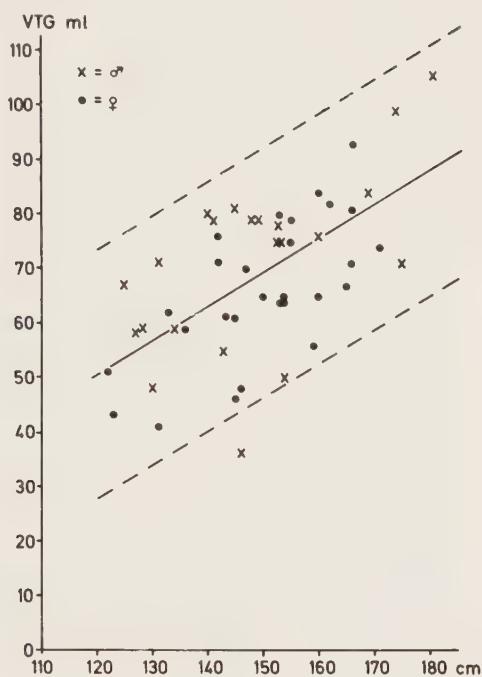


Fig. 1. The relation of VTG to height in healthy children aged 7 to 16. RSD = 11.6, $r = 0.62$, $y = H \times 0.63 - 25.1$

ximum expiration were recorded until at least two acceptable curves were obtained, and the highest readings of VC and FEV₁ were used. All volumes were corrected to BTPS conditions. The same laboratory nurse assisted during the entire study.

Standard statistical methods [13] were used. The error of a single determination, e , was calculated according to Dahlberg [7] from:

$$e = \sqrt{\frac{\sum (X_1 - X_2)^2}{2n}}$$

Results

We found no sex-linked differences in height (± 2.5 cm), static and dynamic spirometric variables, WOV, and VTG in children younger than 15. We presumed that these measured variables are correlated to height in all subjects, including the older ones. This is consistent with the relations shown in Figure 1, and thus the whole material was pooled. The results of the spirometric measurements, nitrogen washout, and VTG are shown in Table 2. The children showed significantly higher FRC ($p < 0.01$), significantly lower LCI ($p < 0.01$), and probably lower FEV% ($p < 0.05$) as compared to the reference values of Kjellman [10]. In the subgroup of 16 children where a double determination was made, the mean VTG was 62 ml with an error of a single determination, reproducibility, of 6.0 ml. The variance (V) was 9.7%. Mean VTG/TLC% was 1.7 with $e = 0.16$ and $V = 9.3\%$. The VTG/VC% showed an average of

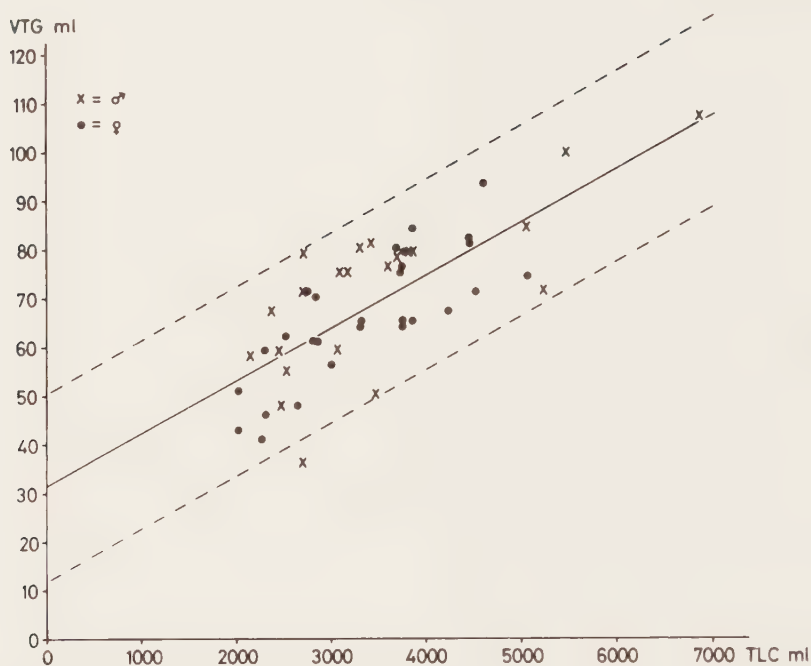


Fig. 2. The relation of VTG/TLC in healthy children aged 7 to 16. RSD=9.7, $r=0.75$, $y=0.011 \times \text{TLC} + 30.79$

Table 2. Mean, SD, and SE of the spirometric variables, WOV, and VTG of 50 healthy children. A=absolute values; B=percent of predicted normal values (10). The VTG is expressed in ml, the remaining volumes in liters.

	VC	TLC	FRC	RV	FEV ₁	FEV%	LCI	WOV	VTG	VTG/ TLC%	VTG/ VC%
A											
Mean	2.81	3.43	1.50	0.62	2.34	82.9	7.69	11.5	68.4	2.1	2.5
SD	0.82	1.00	0.49	0.28	0.76	7.5	1.10	3.7	14.6	0.4	0.5
SE	0.12	0.14	0.07	0.04	0.04	1.1	0.16	0.5	2.1	0.1	0.1
B											
Mean	101.4	100.5	106.9	102.6	96.8	96.0	94.2	104.0			
SD	11.4	13.1	19.1	40.6	12.6	9.0	13.4	21.2			
SE	1.6	1.8	2.7	5.7	1.8	1.3	1.9	3.0			

2.2 with an e of 0.22 and $V=10.4\%$. VTG was correlated to height (H), H^3 , TLC, $\sqrt{\text{TLC}}$, VC, FEV₁, WOV, FRC, weight, and age.

With the exception of the relation to weight and age, all correlations were positive with r values of more than 0.60. The correlation to H was $r=0.62$ (Fig. 1) and to H^3 , 0.63. The highest correlations were found to TLC ($r=0.75$) (Fig. 2) and to $\sqrt{\text{TLC}}$ ($r=0.76$). Figures 1 and 2 show the relation of VTG to height (H) and to TLC, respectively, and can be used to obtain predicted values of VTG.

Discussion

VTG is defined as the volume of N_2 expressed as air mobilized during rebreathing with maximal breaths at the end of the N_2 washout [11]. It might include some slowly ventilated air spaces, since rebreathing starts at the end of an expiration with a FN_2 of 2%. Hence the VTG, as defined here, is only the mobilizable VTG and might be smaller than the true VTG detectable only by a body plethysmograph [1]. Mobilization of VTG requires that a transpulmonary pressure high enough to re-open closed airways be created by maximal inhalations. The VTG might thus be underestimated in severe broncho-obstruction or emphysema. However, the VTG test is mainly useful for detecting subclinical lung disease when earlier applied methods often fail [6, 14]. It is not indicated in subjects with pronounced disease, unless there is a need to quantify the volume of mobilizable VTG. The value of the VTG test in early emphysema or smoker's lung [11] is yet not established. In childhood subclinical asthma, the test appears more sensitive than FEV_1 , LCI, and WOV in detecting the disease [14], and in contrast to the FEV_1 test (Fig. 3), it does not provoke bronchospasm in sensitive children.

The mean values and the SD of the spirometric measurements in the present material are fairly close to those given by Polgar and Promadhat [12] and Kjellman [10]. The mean values of lung function tests were close to 100% for all variables except FRC, $FEV\%$, and LCI. Our subjects may have been less relaxed than those of Kjellman [10], which might explain the higher FRC which we recorded; TLC and

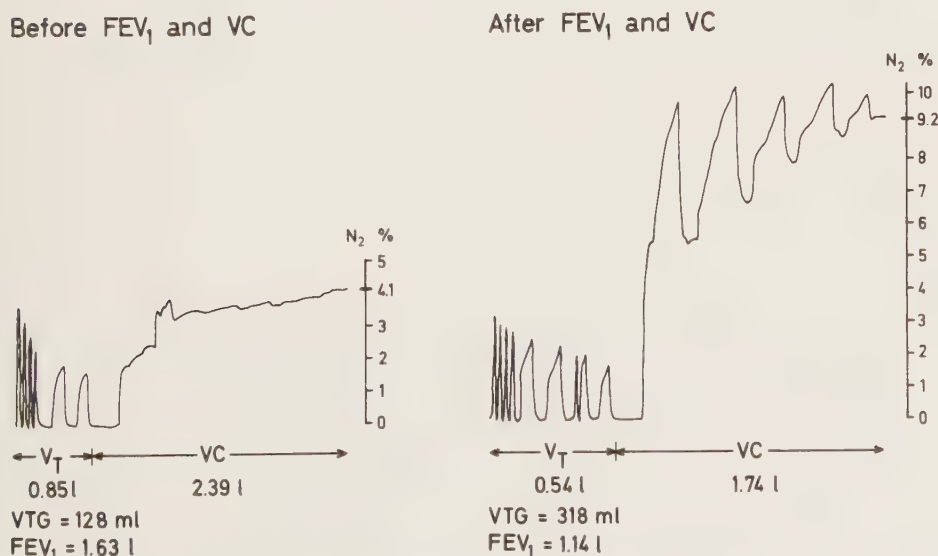


Fig. 3. The end of the nitrogen washout curves and VTG rebreathing before and after FEV_1 and VC in a child with a history of asthma. The child had no subjective signs of asthma before the FVC measurement but did have a subjective feeling of tightness in his chest but no wheezing afterward. Before the test, VTG was 128 ml (+6.2 SD); after, it was 318 ml (+22.6 SD). Kymograph speed before rebreathing was 4 cm/min and during rebreathing, 20 cm/min. N_2 concentration in the rebreathing bag is marked on top of each scale

RV were the same. The lower LCI is a consequence of the higher FRC and the correction for valve dead space. The difference in FEV% is only probably significant, and like the other differences, it may at least partly be due to the rather small number of subjects in Kjellman's series [10] and in the present study. All differences were small from a practical point of view. Kjellman [10] found that WOV is well correlated to height ($r=0.80$), which was also the case in our subjects ($r=0.82$).

The errors of a single determination of VTG, VTG/TLC%, and VTG/VC% were only 6 ml, 0.16%, and 0.22%, respectively. These errors were about 10% of the mean values of the group. The errors found must therefore be regarded as small and the reproducibility of VTG, VTG/TLC%, and VTG/VC% as quite good. The error of a single determination in these children corresponds well to a preliminary study of healthy and diseased adults, in whom it was 12 ml [6]. VTG showed a good correlation to TLC (Fig. 2) and also a fairly good one to height. Thus, in healthy subjects, VTG was more dependent on lung size than on height. In asthmatics and in patients with emphysema, the TLC is abnormal; however, this abnormality seldom is so great that it influences the sensitivity of the tests.

In comparison to other measurements of lung function in children, VTG and VTG/TLC% appeared to be reproducible and predictable with high accuracy. Recent literature has claimed that FEV₁ is a very sensitive test for detection of functional changes in asthma [8]. Benatar and König [2] found little difference in sensitivity between FEV₁ and the flow rate in the lower part of the forced vital capacity. Our impression, however, is that the sensitivity of this flow rate is high in early asthma [4, 15]; results from a comparison between VTG and forced expiratory flow at 25% of VC are being prepared (Svenonius et al., in preparation). Bronchospasm is sometimes provoked by forced expirations (Fig. 3); however, this has not been noticed in either clinical or measurable terms following the VTG maneuver. All children 7 and older could perform the test, and we found it possible to test most children as young as 5.

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References

1. Bedell, G. N., Marshall, R., DuBois, A. B., Comroe, J. H., jr.: Plethysmographic determination of the volume of gas trapped in the lungs. *J. Clin. Invest.* **35**, 664–670 (1956)
2. Benatar, S. R., König, P.: Maximal expiratory flow and lung volume changes associated with exercise-induced asthma in children and the effect of breathing a low-density gas mixture. *Clin. Sci. Mol. Med.* **46**, 317–329 (1974)
3. Bouhuys, A., Hagstam, K. E., Lundin, G.: Efficiency of pulmonary ventilation during rest and light exercise. A study of alveolar nitrogen wash out curves in normal subjects. *Acta Physiol. Scand.* **35**, 289–304 (1956)
4. Bouhuys, A., Hunt, V. R., Kim, B. M., Zapletal, A.: Maximum expiratory flow rates in induced bronchoconstriction in man. *J. Clin. Invest.* **48**, 1159–1168 (1969)
5. Bülow, K., Arborelius, M., jr., Christensson, P., Lilja, B.: Volume of trapped gas (VTG) during provoked asthma and after inhalation of salbutamol. *Scand. J. Respir. Dis. (Suppl.)* **101** (1977)
6. Bülow, K., Arborelius, M., jr., Christensson, P., Lilja, B.: Changes in volume of trapped gas in the lungs during provoked asthma followed by β_2 -receptor stimulation. *Respiration* **6**, 19–27 (1978)

7. Dahlberg, G.: Statistical methods for medical and biological students, pp. 122 – 132. London: George Allen & Unwin Ltd., 1974
8. George, R. B., Conrad, S. A., Light, R. W.: Relative value of tests used to measure bronchodilator response. *Chest* **73**, (Suppl.) 989 – 990 (1978)
9. Karlberg, P. et al.: I. Physical growth from birth to 16 years and longitudinal outcome of the study during the same age period. In: The somatic development of children in a Swedish urban community. A prospective longitudinal study. *Acta Paediatr. Scand. (Suppl.)* **258**, 7 – 76 (1976)
10. Kjellman, B.: Ventilatory efficiency, capacity and lung volumes in healthy children. *Scand. J. Clin. Lab. Invest.* **23**, 19 – 29 (1969)
11. Lilja, B., Arborelius, M., Jr, Janzon, L., Lämsimies, E., Lindell, S. E.: The volume of trapped gas, closing volume and pulmonary gas exchange in smokers and non-smokers aged 60. *Scand. J. Respir. Dis. (Suppl.)* **95**, 48 – 59 (1976)
12. Polgar, G., Promadhat, V.: *Pulmonary Function Testing in Children; Techniques and Standards*. Philadelphia: W. B. Saunders, 1971
13. Snedecor, G. W.: *Statistical Methods*, 5th ed, pp. 35 – 66, 122 – 193. Ames, Iowa: The Iowa State College Press, 1956
14. Svenonius, E., Lecerof, H., Lilja, B., Arborelius, M., jr.: The volume of trapped gas: A new and sensitive test for the detection of exercise-induced bronchospasm in children. *Acta Paediatr. Scand.* **67**, 583 – 589 (1978)
15. Zapletal, A., Motoyama, E. K., Gibson, L. E., Bouhuys, A.: Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics* **48**, 64 – 72 (1971)

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Flow-Volume Measurements with a Spirometer

Results from Healthy Children

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Abstract. All information in the flow-volume curve should be present in the forced expired volume curve recorded with a high fidelity spirometer. This hypothesis was tested by comparing $\dot{V}_{\max 25}$ (the flow at RV+25% VC) measured from flow-volume curves obtained with a pneumotachograph system and an X-Y-oscilloscope with $\dot{V}_{\max 25}$ measured from a forced expirogram recorded with a high fidelity spirometer. The flow at RV+25% VC was derived by a line drawn through two points on the spirogram at ± 0.1 sec. from this volume. Measurements were made on repeated identical FEV blows with different flow rates from an FEV simulator and on exhalations with various flows from two healthy volunteers. The reproducibility was equally good with both methods but a constant error was present in the pneumotachograph measurements (calibration error). In 50 healthy children $\dot{V}_{\max 25}/\text{TLC}$ obtained with a spirometer had the same magnitude and variability as found by previous authors using conventional flow volume records from a pneumotachograph system.

Key words: Lung function in children – Maximum expiratory flow rates – $\dot{V}_{\max 25}/\text{TLC}$ ratio – FEV simulator

Introduction

The flow rate in the lower part of the forced expired volume (FEV) for example at 25% of the vital capacity (VC) has been claimed to be a sensitive measure of small airways disease [3]. This maximum flow rate ($\dot{V}_{\max 25}$) is commonly measured on a flow-volume curve obtained with a pneumotachograph and volume is integrated from a flow signal.

Provided that the forced exhaled volume (FEV) curve is recorded with a high fidelity spirometer [2], it should contain all the information within the flow-volume curve. Flow can be derived from the slope of the curve at any volume. The derivation of flow from volume change per time has several advantages over integrating volumes from flow signals:

1. Volume and kymograph speed of spirometers are easy to calibrate and thereafter usually stable while the pneumotachograph with integrator and recording systems are difficult to calibrate and calibration has to be checked repeatedly [4].
2. Spirometers are basic equipment not only in respiratory laboratories and relatively cheap while systems for recording flow-volume curves are expensive [6, 9, 11].
3. Pneumotachographs are sensitive to changes in gas composition and not always linear.
4. If it can be proved that flows derived from spirometer curves are equivalent to those obtained from flow-volume curves, it would be possible to use old information on FEV-curves for follow-up studies of flow at the more sensitive part of the curve [3, 12].

In spite of these advantages we have not been able to find any reports on flow measurements with spirometers as compared to pneumotachograph systems.

We therefore compared the accuracy of the measurements of the flow at 25% of VC ($\dot{V}_{\max 25}$) measured with a pneumotachograph to those derived from FEV-curve recorded with a high fidelity spirometer [2]. Values for $\dot{V}_{\max 25}$ from 50 healthy children as measured from FEV-curves are also presented.

Material

One 51 year-old male nonsmoking MD and one nonsmoking 46 year-old female MD served as volunteers for FEV blows. Fifty healthy children in the age group 7 to 16 years served as normal population for reference values for $\dot{V}_{\max 25}$ as measured with the spirometer [8]. Informed consent to partake was given by all parents.

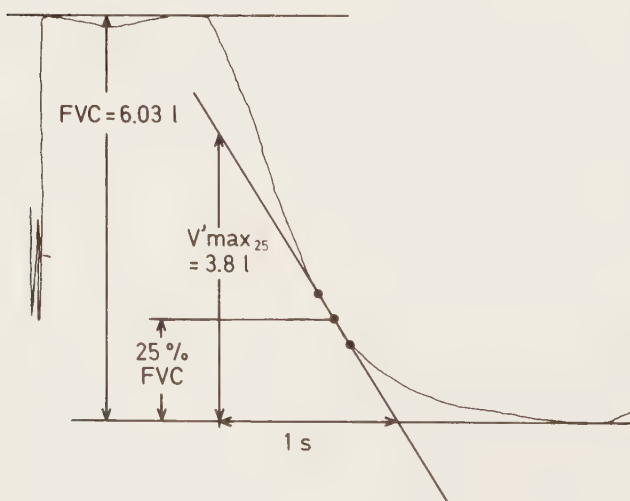


Fig. 1. FEV-curve from a boy aged 16 recorded with a high fidelity spirometer. The forced vital capacity (FVC) was 6.03 l. The flow at 25% of VC ($\dot{V}_{\max 25}$) 3.8 l was calculated by derivation of the flow at this point ± 0.1 sec by the tangent through two points marked on the curve using a sharp pencil. These points are amplified in the figure as they are too small to be seen in the original size.



Fig. 2. Two superimposed flow-volume curves photographed from the X-Y storage oscilloscope when the FEV simulator had delivered two blows with fixed volumes and flow rates to the pneumotachograph system.

Methods

The flow-volume curves were recorded with an X-Y storage (Tectronix 603) oscilloscope connected to a factory calibrated (Fleisch No 3) pneumotachograph, a part of a body plethysmograph system (Siregnost FD 91, Siemens-Elema AS, Erlangen, West-Germany). This included a high quality integrator for volume and a tilting water manometer increasing calibration accuracy 15 times. Before the measurements the pneumotachograph system was calibrated with this manometer according to the manual. The flow-volume curves on the oscilloscope were photographed with a Polaroid CR 9 Land Camera and the maximal flow at 25% of the VC ($\dot{V}_{\max 25}$) was measured.

$\dot{V}_{\max 25}$ was calculated on the FEV-curve recorded with a high fidelity spirometer (kymograph speed 500 mm/sec.; volume calibration 1 mm = 50 ml) by subtracting 75% of the FEV from the top of the FEV-curve and by derivation of the average flow at that height ± 0.1 sec. (5 mm) by a thin line through two points thus marked on the curve (Fig. 1) using a sharp pencil. The two different methods were compared statistically with Student's paired t-test and by correlation of the results by common procedures [7].

Protocol. Exactly reproducible simulated forced expiratory volumes (FEV) were delivered by an FEV simulator consisting of a plexiglass drum with a volume of 25 liters. It was filled with compressed air to a predetermined pressure which was measured by a precision manometer. An electrically controlled valve released the compressed gas through a convenient resistor. The delivered volumes and flows were perfectly reproducible (Fig. 2). The apparatus will be described in detail elsewhere [1]. Two consecutive blows at four different volume-flow rates were recorded first with the pneumotachograph and then with the spirometer.

After a repeated calibration according to the manual of the pneumotachograph two more paired blows at different volume-flow rates were recorded (o in Fig. 3). To study reproducibility six blows were recorded with each apparatus at pressures in the FEV simulator of 13.3 and 26.7 kPa (Table 1). Finally, the pneumotachograph was coupled in series to the mouthpiece of the spirometer and a series of 13 voluntarily varied maximal and submaximal blows were delivered by the two MD's and simultaneously recorded with the two systems (x in Fig. 3).

FEV-curves were also obtained from 28 healthy girls and 22 healthy boys [8] and $\dot{V}_{\max 25}$ was calculated from the spirometer curves.

All measurements were corrected to BTPS conditions.

Table 1. Reproducibility of $\dot{V}_{\max 25}$ /sec. with the two methods. FEV-curves delivered by a FEV simulator with a pressure of 26.7 and 13.3 kPa

	26.7 kPa		13.3 kPa	
Spirometer n=6	m	3.578	m	2.505
	SD	0.034	SD	0.062
Pneumotachograph n=6	m	3.422	m	2.380
	SD	0.040	SD	0.000
Difference		0.156 (4.4%)		0.125 (5.0%)

Results

The results are presented in Figure 3. It is obvious that the relation between the measurements with the spirometer and the pneumotachograph was good, $r=0.98$. Repeated measurements by another technician on the flow-volume curves gave different results only at two measurements with a maximum difference of 0.25 mm or 125 ml/sec with the used calibration. Repeated plotting and measurements on the FEV-curve rendered a maximum difference of 60 ml/sec. The difference between the line of identity and the regression line (Fig. 3) seems to have been caused by an

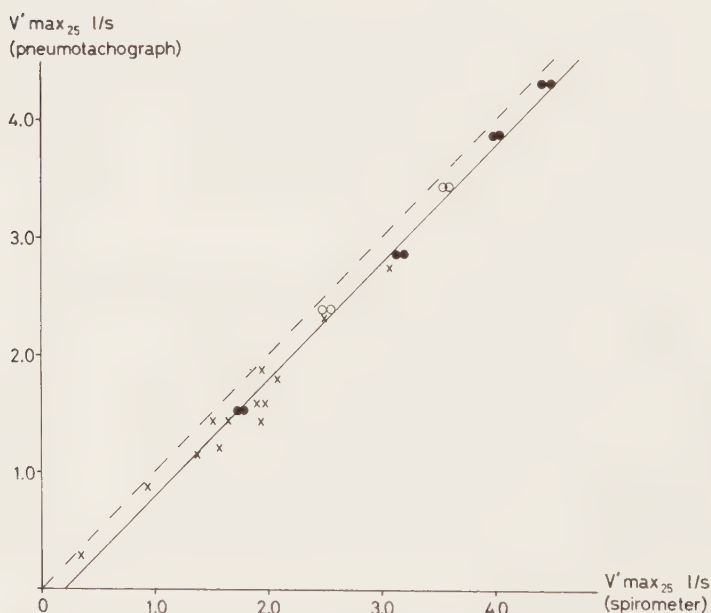


Fig. 3. The relationship between $\dot{V}_{\max 25}$ recorded with the pneumotachograph and calculated from the spirometer curve. Eight measurements were made after calibration (marked ●) and four after recalibration (marked ○) of the pneumotachograph system when the FEV simulator delivered blows with a pressure of 6.7, 13.3, 20, 26.7, 33.3 and 40 kPa. The values fell on the same regression line. $RSD=0.09$, $r=0.996$. $\dot{V}_{\max 25}$ (pneumotachograph) = $\dot{V}_{\max 25}$ (spirometer) $\times 0.994 - 0.190$. The dashed line is the line of identity. Thirteen blows from two volunteers are marked with X.

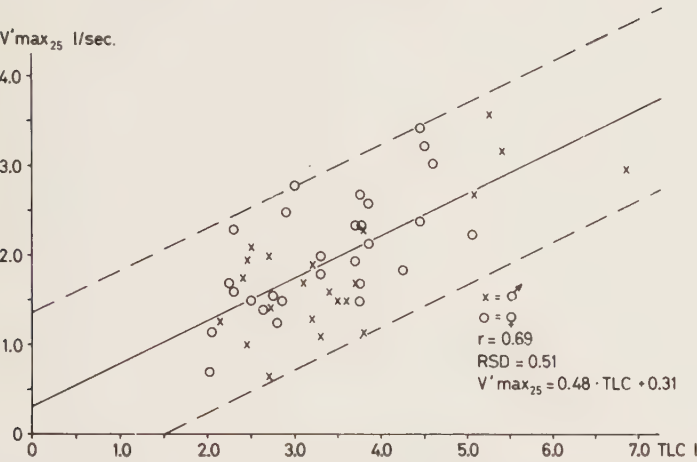


Fig. 4. $\dot{V}_{\max 25}$ of the 22 boys and 28 girls, all healthy, in relation to their total lung capacity (TLC), $r=0.69$.

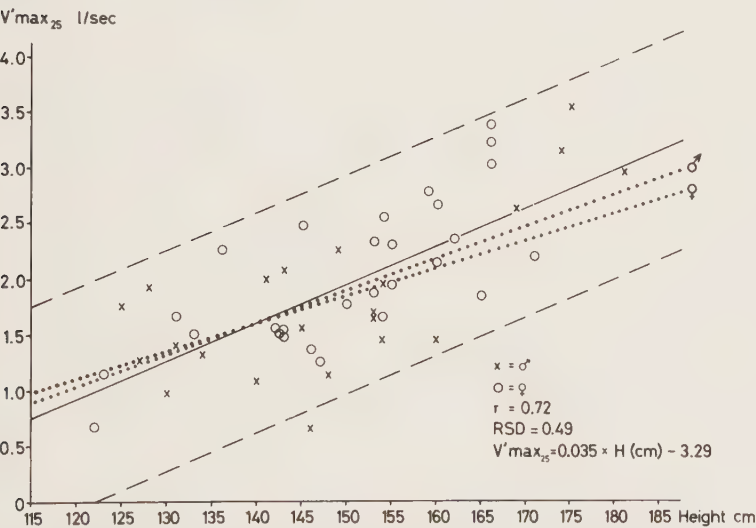


Fig. 5. $\dot{V}_{\max 25}$ of the healthy children in relation to their height (H). $r=0.72$. The regression lines for boys (♂) and girls (♀) from Zapletal et al. [12] are included for comparison (dotted lines).

Table 2. The values of $\dot{V}_{\max 25}$ (l/sec) and $\dot{V}_{\max 25}/\text{TLC}$ from the healthy children, 22 boys and 28 girls calculated from their spirometer curves

	$\dot{V}_{\max 25}$		$\dot{V}_{\max 25}/\text{TLC}$	
	Boys n = 22	Girls n = 28	Boys n = 22	Girls n = 28
$\bar{m}$	1.82	2.04	0.53	0.61
SD	0.74	0.66	0.16	0.16

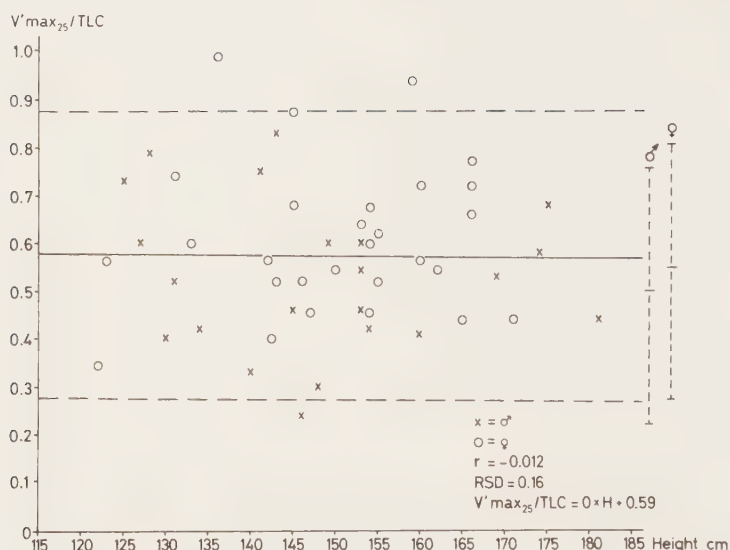


Fig. 6. $\dot{V}_{\text{max}25}/\text{TLC}$ of the healthy children in relation to their height (H). $r = -0.012$. The average $\dot{V}_{\text{max}25}/\text{TLC}$ was 0.57 ± 0.16 . Values from Zapletal et al. [12] are included to the right for comparison.

error in the factory calibration of the pneumotachograph and was up to 190 ml/s. The reproducibility of the flows from the FEV simulator was good (Fig. 2) and virtually all the variation in the measurements was due to differences caused by the plotting and measuring.

The differences between measurements of $\dot{V}_{\text{max}25}$ were somewhat larger when the measurements were made on the voluntarily varied blows from the two adult subjects (Fig. 3). Still there was no statistically significant difference between the results with the two methods.

The reproducibility of the two methods is illustrated by the 6 measurements made by each method at two different flows (Table 1). The standard deviation of the flow-volume method was very small and that of flows measured from the FEV-curves close to ± 50 ml/sec.

Table 2 presents $\dot{V}_{\text{max}25}$ measured from spirometric curves in healthy children in absolute values and as fractions of the TLC. Figures 4 and 5 present $\dot{V}_{\text{max}25}$ in relation to TLC and height, respectively. There was a good positive relation to both these parameters ($P < 0.001$). Figure 6 shows the lack of relation of $\dot{V}_{\text{max}25}/\text{TLC}$ to height.

It is obvious that even if girls show slightly higher values than boys of the same height, the values are so scattered that there was no significant difference ($P > 0.2$). The average value for both boys and girls was $\dot{V}_{\text{max}25}/\text{TLC} = 0.57 \pm 0.16$.

Discussion

Previous attempts have been made to measure flow from spirometric curves [5], but to our knowledge no comparison between flow values obtained with a pneumota-

chograph and a spirometer has been published. The reproducibility of the two methods for measuring flow at RV +25% of VC is best illustrated by the experiments made with the FEV simulator. The reproducibility appears somewhat better with the pneumotachograph system, but this is partly visual. A distance cannot be measured with a ruler with better resolution than ± 0.1 mm. Hence, if a series of $\dot{V}_{\max}25$ s is measured, as presented in table 1, one is inclined to regard all measurements with differences of up to 0.2 mm as being identical. Still, with the calibration we used, such a small difference gives an inherent inexactness of the measurement of 0.054 l/sec.

With the same accuracy in the measurements the methodological error with the spirometer method would be ± 0.055 l/sec, which coincides quite well with the errors actually found in Table 1. On the other hand, the calibration factor for the spirometer recording is fixed and the average value of the recorded flow, 3.58 l/sec, coincides to the second decimal with the delivered flow. Hence, the factory calibration error of the pneumotachograph was between 125 and 190 ml/sec (Table 1 and Fig. 3) which stresses the necessity for calibrating pneumotachographs with known airflows [3].

We confirmed the results of Zapletal et al. [12] that $\dot{V}_{\max}25/\text{TLC}$ was not related to height (Fig. 6). Furthermore, the $\dot{V}_{\max}25/\text{TLC}$ in our population of healthy children was similar to that reported by Zapletal et al. [12]. We confirmed that girls had somewhat higher flows than boys with the same lung size [10, 12]. The small differences in mean values and SD from those reported by Zapletal et al. [12] could well be explained by the limited number of children. Their results are included in Figures 5 and 6 for comparison.

The coefficients of variation of $\dot{V}_{\max}25/\text{TLC}$ as found by us (30% in boys and 26% in girls) are not larger than those given by other authors as cited by Taussig [10].

We conclude that $\dot{V}_{\max}25$ can be measured exactly and reproducibly from an FEV-curve recorded with a high fidelity spirometer. $\dot{V}_{\max}25/\text{TLC}$ in healthy children measured with this method has the same magnitude and variability as described by other authors using pneumotachograph systems [12].

Considering the time lost in repeated calibrations of pneumotachograph system and photographing the curves, calculating from spirometry curves is not more time-consuming or difficult.

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References

1. Arborelius M Jr, Carlsson S, Ringqvist I (unpublished ms.) An apparatus for forced expiratory volume calibrations
2. Berglund E, Birath G, Bjure J, Grimby G, Kjellmer I, Sandqvist L, Söderholm B (1963) Spirometric studies in normal subjects. I. Forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand* **173**: 185 – 192
3. Bouhuys A, Hunt VR, Kim BM, Zapletal A (1969) Maximum expiratory flow rates in induced bronchoconstriction in man. *J Clin Invest* **48**: 1159 – 1168
4. Bouhuys A, Virgulto JA (1978) Calibration of flow-volume curves. *Lung* **155**: 123 – 130

5. Mazumdar BN, Desai CA, Shah NC (1976) A comparative study of a few tests of dynamic lung function. *Indian J Physiol Pharmacol* **20**: 22 – 26
6. Nelson DC, Burrows B, Knudson RJ (1973) A device for recording flow and volume data in population surveys. *J Appl Physiol* **35**: 304 – 306
7. Snedecor GW (1966) *Statistical Methods*, Ames, Iowa: The Iowa University Press
8. Svenonius E, Kautto R (1979) The volume of trapped gas in healthy children, aged 7 – 16. *Lung* **156**: 71 – 77
9. Takishima T, Sasaki T, Takahashi K, Sasaki H, Nakamura T (1972) Direct-writing recorder of the flow-volume curve and its clinical application. *Chest* **61**: 262 – 266
10. Taussig LM (1977) Maximal expiratory flows at functional residual capacity: A test of lung function for young children. *Am Rev Resp Dis* **116**: 1031 – 1038
11. Virgulto J, Bouhuys A (1973) Electronic circuits for recording of maximum expiratory flow-volume (MEFR) curves. *J Appl Physiol* **35**: 145 – 147
12. Zapletal A, Motoyama EK, van de Woestijne KP, Hunt VR, Bouhuys A (1969): Maximum expiratory flow-volume curves and airway conductance in children and adolescents. *J Appl Physiol* **26**: 308 – 316

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Volume of trapped gas and maximum flow at 25% of vital capacity in exercise-induced asthma

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Exercise-induced asthma (EIA) may serve as a model for disease causing the narrowing of small airways. The volume of trapped gas (VTG) proved superior to both static spirometric volumes, forced expiratory volume in one second (FEV_1) and FEV_1 as a percentage of vital capacity ($FEV\%$) for detecting EIA in children, while nitrogen wash-out data like lung clearance index (LCI), which should be sensitive to small airways disease, were somewhat less sensitive [1]. However, we did not compare VTG with another test considered sensitive to small airways disease, the maximum flow rate at 25% of vital capacity ($V'_{max_{25}}$), commonly expressed in parts of total lung capacity (TLC) [2, 3].

Material

The patients were 6 girls and 10 boys, 6-16 years old, with a history of EIA. Controls were 10 healthy children of the same age group. If a participant had any signs or symptoms of active asthma or infection the investigation was postponed.

Methods

Static and forced spirometry and nitrogen wash-out were performed after 30 minutes' rest (BE), after running for 6 minutes on a treadmill aiming at a pulse rate of 170 or more (AE), after 2 puffs of salbutamol from a pressurized aerosol (AS) and after another minute of running (ASE). VTG was defined as the volume of nitrogen mobilized by rebreathing of oxygen with vital capacity (VC) breaths after a nitrogen wash-out to 2%, but expressed as air:

$$VTG = \frac{(TLC \times FN_2ER) - (FRC \times 0.02)}{0.80}$$

(where FN_2ER = nitrogen concentration in a rebreathing bag at the end of rebreathing and FRC = functional residual capacity.) $V'_{max_{25}}$ was calculated from the forced expiratory volume curves recorded with a high fidelity spirometer by drawing a fine line through 2 points marked on the curve ± 5 mm (0.1 second) from the residual volume (RV) + 25% of vital capacity (VC) (Fig. 1). $V'_{max_{25}}$ was estimated just as accurately by this method as from the usual flow-volume curves obtained by pneumotachygraphy and XY-oscilloscopy [4]. TLC was calculated

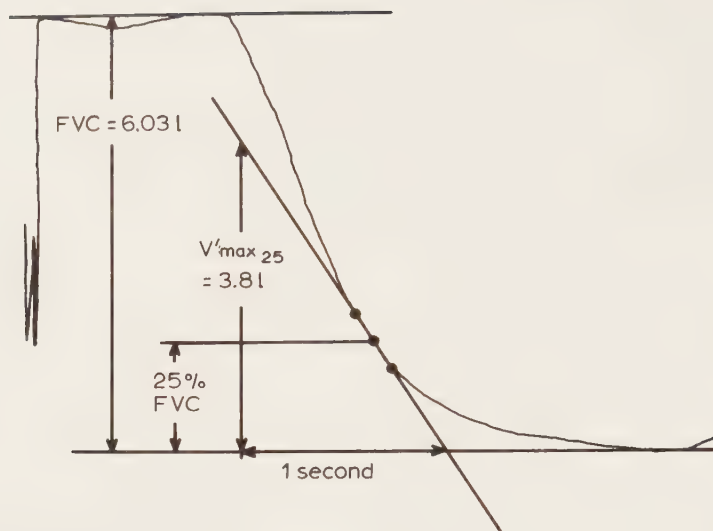


Fig. 1: The method of calculating $V'_{max_{25}}$ by drawing a line through 2 dots on the FEV curve ± 0.1 second from $RV + 25\%$. When applied practically the dots are made with a sharp pencil and are too small to visualize on a reproduction showing the whole curve.

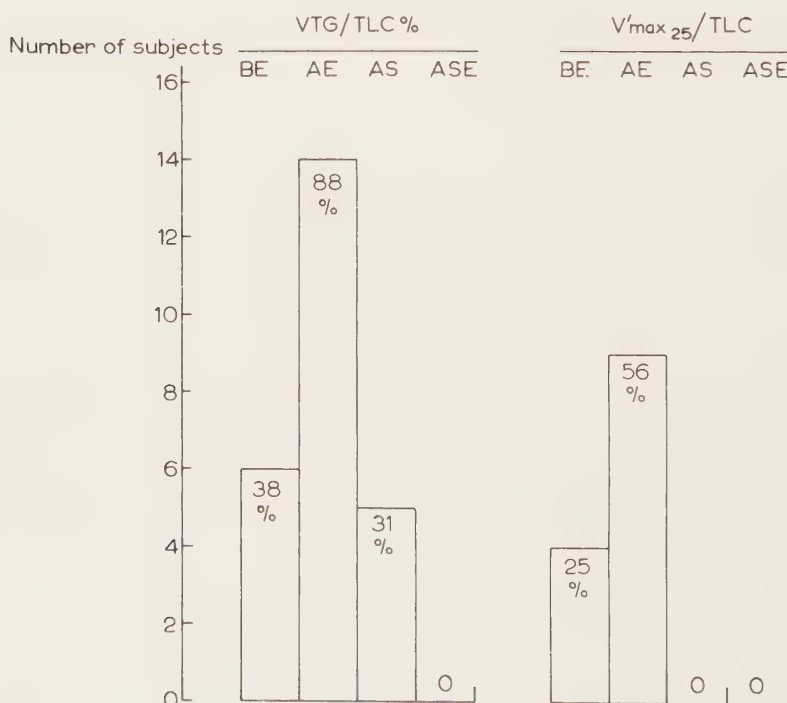


Fig. 2: Number of subjects showing a deviation in the pathological direction of at least 2 SD from the predicted normal value. Reference material from 50 healthy children in the same age group. VTG consequently denotes more subjects as abnormal during all phases of the experiment.

Table: Mean value and standard deviation of VTG and $V'_{\max_{25}}$ and the same related to TLC in 16 children with a history of exercise-induced asthma and 10 healthy children of the same age.

	Asthmatic children				Healthy children			
	BE	AE	AS	ASE	BE	AE	AS	ASE
VTG ml	109	271***	103	82*	70**	73**	69*	73
SD	36	193	47	21	19	16	16	24
VTG/TLC%	2.7	5.9***	2.4	2.0**	1.9**	1.9***	1.8*	1.9
SD	0.8	2.5	0.7	0.4	0.4	0.3	0.4	0.3
$V'_{\max_{25}} \text{ l} \times \text{s}^{-1}$	1.30	1.04**	1.72***	1.71***	2.29***	2.26***	2.32*	2.45**
SD	0.40	0.32	0.45	0.49	0.88	0.76	0.82	0.80
$V'_{\max_{25}}/\text{TLC}$	0.33	0.26**	0.43***	0.42**	0.60***	0.59***	0.60**	0.63***
SD	0.12	0.12	0.11	0.11	0.15	0.15	0.12	0.15

Asterisks under 'asthmatic children' denote significance of changes in relation to BE. Asterisks under 'healthy children' denote significance between asthmatic and healthy children. No changes in the healthy children were significant. * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

from the inspiratory reserve volume at spirometry and FRC obtained from the multiple breath nitrogen wash-out.

Results

Results are presented in the Table and Figures 2 and 3. $V'_{\max_{25}}/\text{TLC}$ and $V'_{\max_{25}}$ both decreased significantly after exercise ($P < 0.01$) while the increase in VTG/TLC% or VTG/VC% was highly significant ($P < 0.001$). The change in VTG reached the same significance as that of $V'_{\max_{25}}$. After salbutamol and salbutamol plus exercise $V'_{\max_{25}}/\text{TLC}$ increased highly significantly ($P < 0.001$) in relation to the pre-exercise values, while the decrease in VTG/TLC% was not significant after salbutamol but was after salbutamol plus a short exercise ($P < 0.01$). $V'_{\max_{25}}/\text{TLC}$ was highly significantly lower in the asthmatic than in the healthy children before exercise, after exercise and after the second exercise ($P < 0.001$), while the difference was smaller, but still significant after salbutamol ($P < 0.01$). VTG/TLC% was significantly higher than in the controls before exercise, highly significantly higher after exercise, probably higher after salbutamol and in the normal range after the second short exercise.

Discussion

It appears that both methods would be equally sensitive for disclosing disease in a clinical group of patients. In the single patient abnormality must be defined as a deviation in the pathological direction of 2 standard deviations or more from the

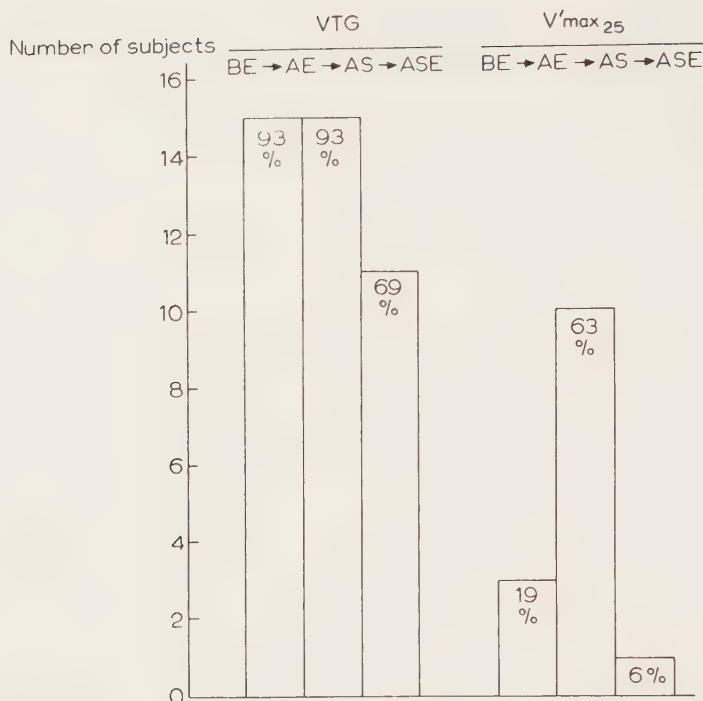


Fig. 3: Number of subjects showing a change larger than twice the error of a single determination in VTG or $V'_{\max_{25}}$ in the expected direction between BE and AE (first column), AE and AS (second column) and AS and ASE (third column).

predicted value found in healthy subjects [4]. VTG/TLC% disclosed disease in all but 2 cases after exercise while $V'_{\max_{25}}$ did not do so in 7 subjects. A change larger than 2 errors of a single determination of the applied test may be considered as not due to normal variations inherent in the method (see Fig. 3). According to this criterion 15 out of 16 patients showed a significant increase in VTG after running, but $V'_{\max_{25}}$ decreased significantly in only 3 out of 16. Salbutamol induced significant decreases in VTG in 15 subjects, while 5 out of 16 showed increased $V'_{\max_{25}}$. The division by TLC was omitted in this comparison in order to avoid the influence of changes in TLC. After the second exercise one out of 16 increased $V'_{\max_{25}}$ significantly and in one this decreased. Eleven showed a further decrease in VTG while in 3 this increased. All the latter were, however, well within the normal range, both before and after the last exercise. One subject did not show signs of EIA by VTG, spirometry or nitrogen wash-out but $V'_{\max_{25}}$ showed a large decrease. However, it was difficult to make him perform a good FEV₁-manoeuvre in spite of several attempts and also the best one showed artefacts due to bad cooperation at 25% VC. It must also be noted that only one subject had a $V'_{\max_{25}}$ /TLC above the predicted average before exercise which increased thereafter, and that he was one of the 2 having less than the predicted VTG, which only showed a minor increase after exercise. In 3 other subjects $V'_{\max_{25}}$ did not change or even increased after exercise while VTG increased very much.

Flow-volume curves have been found superior to closing volume [2] and flow resistance [3] for the detection of abnormality in chronic asthma. VTG seems superior to $V'_{\max_{25}}$ for the detection of asthma in individual subjects. However, $V'_{\max_{25}}$ is better than most other tests and equivalent to VTG for separating an asthmatic group from their healthy controls. However, $V'_{\max_{25}}$ seems inferior to VTG for detecting an increase in exercise-provoked bronchospasm, which most probably occurs in small airways.

Summary

The VTG in the lung that can be released by vital capacity breathing at the end of a nitrogen wash-out to 2% N_2 and $V'_{\max_{25}}$ were measured in 16 children with a history of exercise-induced asthma and in 10 healthy controls. Both methods disclosed abnormality in the diseased children with the same significance. However, $V'_{\max_{25}}$ did not change or even increased in 4 children who showed a pronounced increase in VTG. The 2 methods thus seem to be sensitive to different abnormalities in lung function. Obliteration of airways causing increase in VTG would most likely occur in small airways while $V'_{\max_{25}}$ only registers changes in patent airways, whether small or large.

References

1. Svenonius, E., Lecerof, H., Lilja, B. and Arborelius, M. Jr (1978): The volume of trapped gas: a new and sensitive test for the detection of exercise-induced bronchospasm in children. *Acta paediat. scand.*, 67, 583.
2. Cooper, D.M., Doron, I., Mansell, A.L. *et al.* (1974): The relative sensitivity of closing volume in children with asthma and cystic fibrosis. *Amer. Rev. resp. Dis.*, 109, 519.
3. Zapletal, A., Motoyama, E.K., Gibson, L.E. and Bouhuys, A. (1971): Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics*, 48, 64.
4. Svenonius, E., Kautto, R. and Arborelius, M. Jr (1979): Flow volume measurements with a Bernstein spirometer. Results from healthy children. (In manuscript.)

Lung Function Studies in Children with Allergic Rhinitis

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Thirty carefully selected children with seasonal allergic rhinitis but without history or signs of lung involvement were examined clinically and by lung function tests during the pollen season as well as in the pollen-free season. During the pollen-free season the children had – if anything – slightly better lung function than a healthy control material. During the pollen season the only change was a slight increase in FRC and a decrease in lung clearance index, directly proportional to the change in FRC. Sixteen of the children performed an exercise test in the pollen-free season. A small increase in the volume of trapped gas (VTG) was noted, indicating a subclinical spasm in small airways. Salbutamol inhalation after exercise reduced VTG below base-line values, indicating disappearance of subclinical bronchospasm. Hay fever children thus have a tendency towards bronchospasm after exercise in the pollen-free season, which, however, is of no clinical importance, as their VTG also after the exercise was less (better) than the predicted normal.

Key words: allergic rhinitis; children; exercise test; lung function.

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Allergic rhinitis and asthma are related diseases and the same subjects often have symptoms from their upper airways as well as from their bronchi, when exposed to specific allergens, usually a pollen. However, it is still uncertain whether there is subclinical bronchospasm (6) or bronchial lability (9) in the children *with* allergic rhinitis but *without* a history of wheezing or clinical signs of bronchospasm during the pollen season.

The purpose of this study was to investigate children with seasonal allergic rhinitis by 1) comparing their lung function during the pollen season with their function during a following pollen-free season and 2) evaluating whether an exercise test performed during the pollen-free season provoked an abnormal bronchial response.

MATERIAL AND METHODS

The study should comprise children with pollen-allergic rhinitis but without previous

history of cough and chest tightness or auscultatory signs of asthma during the pollen seasons. Out of 42 consecutive children with allergic rhinitis seen at the outpatient ward 12 children had to be excluded due to clinical asthma as defined above. All the remaining 30 children were within normal limits as regards height and weight. All were allergic to birch and/or grass pollens and had pronounced rhinitis, treated with sodium cromoglycate and/or antihistamines. Fifteen were hyposensitized. Their allergies were verified by skin test and/or RAST. Mean age was 12.4 years (range 8–17).

Procedure

The lung investigations were performed when the children had pronounced rhinitis and when they had been free from symptoms for at least 1 month.

In 16 of the children, randomly selected, lung function was also measured before and after an exercise load and the results were

compared with those from 10 healthy children previously examined with the same methods at our laboratory (14). At the time of all the investigations the children had been free from medications for at least 48 h. Informed consent was obtained from both the children and their parents.

Methods

Spirometry was performed with the aid of a high fidelity spirometer (AB Kifa, Sweden). Static vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were determined. From the FEV -curve the maximal flow at 25% of the VC (V'_{max25}) was also measured (13, 15).

A multiple breath nitrogen wash-out method (2) was used for measuring the functional capacity (FRC) and ventilatory efficiency, expressed as lung clearance index (LCI) = WVO/FRC and wash-out volume (WVO).

The volume of trapped gas (VTG) was also measured (5, 10, 12). VTG in per cent of VC ($VTG/VC\%$) and VTG in per cent of total lung

capacity ($VTG/TLC\%$) were also calculated. According to our earlier routines for provoking exercise-induced asthma (14) the exercise test was performed on a treadmill, and lung function was estimated before exercise and immediately after the exercise. The children then inhaled 200 μ g salbutamol from a dose aerosol and 10 min later a new lung function examination was performed. The exercise load during 6 min (elevation 5° speed 5–8 km/h) aimed at a heart rate of 170 beats/min. The 10 healthy children had been examined in the same manner. Significance of differences between the test was tested by the Student's *t*-test for paired observations or, when appropriate, for different groups.

RESULTS

Table 1 presents lung function data of the children during their pollen-free and pollen seasons in per cent of predicted normal (12) and the change between the two times for examination.

Table 1

Lung function values in 30 children in per cent of predicted normal values during pollen-free, pollen season and the change. The VTG values were significantly smaller (more normal) than VTG values from healthy children (12). The comparison between pollen-free and pollen season is made with paired *t*-test

	During pollen-free season (mean $\pm$ SD)	During pollen season (mean $\pm$ SD)	The change between pollen-free and pollen season (mean diff $\pm$ SD diff)
VC	103.6 $\pm$ 13.3	104.4 $\pm$ 14.1	0.9 $\pm$ 4.8
TLC	104.5 $\pm$ 15.2	107.2 $\pm$ 15.8	2.7 $\pm$ 8.7
FRC	105.6 $\pm$ 19.2	111.6 $\pm$ 19.0	6.0 $\pm$ 15.0*
FEV_1	105.3 $\pm$ 17.6	104.7 $\pm$ 15.3	-0.6 $\pm$ 6.1
$FEV\%$	101.5 $\pm$ 6.8	100.8 $\pm$ 8.8	-0.7 $\pm$ 8.1
V'_{max25}	104.7 $\pm$ 29.6	102.7 $\pm$ 26.4	-2.0 $\pm$ 25.0
V'_{max25}/TLC	98.6 $\pm$ 18.2	95.1 $\pm$ 22.0	-3.5 $\pm$ 22.3
LCI	98.2 $\pm$ 13.7	91.6 $\pm$ 9.3	-6.6 $\pm$ 15.9*
WVO	103.9 $\pm$ 18.4	102.7 $\pm$ 17.3	-1.3 $\pm$ 16.9
VTG	87.0 $\pm$ 22.5**	87.7 $\pm$ 22.9	0.7 $\pm$ 25.4
$VTG/TLC\%$	84.3 $\pm$ 24.0**	84.0 $\pm$ 25.0	-1.1 $\pm$ 24.2
$VTG/VC\%$	85.1 $\pm$ 24.5**	84.7 $\pm$ 24.8	0.5 $\pm$ 25.2

No sign = no change or increase. - Sign = decrease.

* = $P < 0.05$.

** = $P < 0.01$.

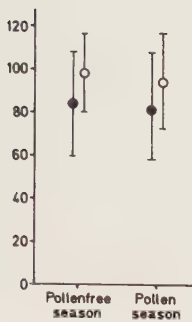


Fig. 1. The mean $\pm$ SD of VTG/TLC% and of $V'_{\max}$ 25/TLC, both in per cent of predicted normal in the 30 children with allergic rhinitis in pollen-free and pollen season. ○ = $V'_{\max}$ 25/TLC. ● = VTG/TLC%.

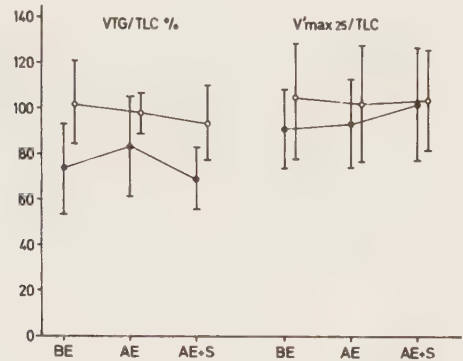


Fig. 2. The mean $\pm$ SD of VTG/TLC% and $V'_{\max}$ 25/TLC exposed in per cent of predicted from 16 children with allergic rhinitis, BE (before exercise), AE (after exercise) and AE + S (after inhalation of salbutamol). Control values in healthy children presented in the same way. ○ = Healthy children. ● = Children with allergic rhinitis.

During the pollen-free season the VTG values were statistically somewhat better (lower) ($P < 0.01$) than in healthy children of the same age. During pollen season FRC was higher ($P < 0.05$) and LCI somewhat lower ($P < 0.05$) compared to pollen-free season.

Fig. 1 shows VTG/TLC% and $V'_{\max}$ 25/TLC in pollen-free and pollen season.

Table 2 shows the results of the exercise test. After exercise (AE) a significantly increased deterioration ($P < 0.05$) in VTG and related variables occurred in the 16 children. In comparison with the values at rest FRC, $V'_{\max}$ 25/TLC ($P < 0.05$), and $V'_{\max}$ 25 ($P < 0.01$) were significantly better after salbutamol (AE + S). In comparison with the examination "after exer-

Table 2

Lung function studies in the 16 hay fever patients in pollen-free season in per cent of predicted normal values before exercise (BE), and the changes after exercise (AE), and after 0.2 mg salbutamol (AE + S). The comparisons between BE - AE, BE - AE + S, and AE - AE + S are made with paired test. In the 10 healthy children no significant changes occurred except for VC in AE - AE + S, which showed mean diff. of -1.4% ($P < 0.001$)

	BE mean $\pm$ SD	BE to AE mean diff $\pm$ SD diff	BE to (AE + S) mean diff $\pm$ SD diff	AE to (AE + S) mean diff $\pm$ SD diff
VC	106.7 $\pm$ 12.6	-0.1 $\pm$ 1.9	0.8 $\pm$ 2.6	0.9 $\pm$ 2.8
TLC	107.5 $\pm$ 12.1	0.8 $\pm$ 4.8	1.8 $\pm$ 5.5	0.9 $\pm$ 6.1
FRC	108.3 $\pm$ 15.7	-1.1 $\pm$ 10.9	-4.9 $\pm$ 8.3*	-3.8 $\pm$ 10.4
FEV ₁	108.7 $\pm$ 15.5	0.1 $\pm$ 3.8	2.2 $\pm$ 4.6	2.2 $\pm$ 4.8
FEV%	101.7 $\pm$ 5.6	0.1 $\pm$ 3.7	1.6 $\pm$ 4.6	1.4 $\pm$ 5.2
$V'_{\max}$ 25	99.8 $\pm$ 21.1	2.9 $\pm$ 11.5	13.5 $\pm$ 18.0**	10.6 $\pm$ 14.5*
$V'_{\max}$ 25/TLC	91.6 $\pm$ 17.3	1.9 $\pm$ 12.2	10.9 $\pm$ 15.2*	8.9 $\pm$ 12.0**
LCI	91.7 $\pm$ 5.8	3.2 $\pm$ 9.2	3.2 $\pm$ 8.6	0.0 $\pm$ 10.4
WOV	100.6 $\pm$ 14.5	0.6 $\pm$ 15.3	-1.6 $\pm$ 12.0	-2.1 $\pm$ 11.5
VTG	77.0 $\pm$ 20.9	10.6 $\pm$ 16.4*	-3.6 $\pm$ 18.0	-14.3 $\pm$ 16.9**
VTG/TLC%	73.4 $\pm$ 20.3	10.0 $\pm$ 15.7*	-4.2 $\pm$ 16.1	-14.2 $\pm$ 15.8**
VTG/VC%	72.2 $\pm$ 19.5	10.3 $\pm$ 16.5*	-3.8 $\pm$ 17.5	-14.1 $\pm$ 15.5**

No sign = unchanged or increase. - Sign = decrease.

* = $P < 0.05$.

** = $P < 0.01$.

cise" the values after salbutamol (AE + S) showed a decrease in VTG ($P < 0.01$), while $V'_{\max 25}$, and $V'_{\max 25}/TLC$ increased, ($P < 0.05$) and ($P < 0.01$), respectively. The healthy children examined in exactly the same way did not show any significant changes in relation to exercise and salbutamol (14). Fig. 2 is a graphical presentation of VTG/TLC% and $V'_{\max 25}/TLC$ in the rhinitic and healthy children.

DISCUSSION

It must be stressed that all deviations from normal or normal reactions to exercise or salbutamol, although some were significant statistically, were small and probably without clinical significance. The children with hay fever had slightly better lung function variables than the healthy children. However, they were selected from a larger material containing children with clinical asthma, and asthma may occur in those having basic lung function below the average.

Brown et al. (3) reported that hay fever patients frequently demonstrate a diminished vital capacity during the pollen season. They also found that in "three out of four patients the respiratory tract reacted as a single organ irrespective of the seat of the majority of symptoms of which the patients complained". Fish et al. (8) found that metacholine aerosol produced bronchoconstriction both in allergic subjects with asthma and in those with hay fever, as well as in non-allergic subjects. The sensitivity to metacholine was different in the three groups and the authors suggested that there is a hypersensitivity of both large and small airways in asthmatics but only in the large airways in patients with allergic rhinitis.

The non-significant decrease in FEV_1 , as well as the increase in FRC, in our subjects during the pollen season (Table 1) might indicate a slight involvement of large airways in some subjects. Bruce et al. (4) found in their study of ragweed-asthmatic patients and ragweed-hay fever patients, that the specific airway conductance (S_{Caw}) decreased in both groups after provocation with ragweed extract. Doggett et al.

(6) found that persons with allergic rhinitis had bronchial lability and small airways obstruction shown by a reduction in the maximum mid-expiratory flow rate (FEF 25–75%) and $V'_{\max 25}$. Twenty patients were also examined after exercise and 13 of them developed elevated specific airway resistance and nine had a reduction in FEF 25–75%. However, in this abstract the patient material is poorly defined. Rachelefsky et al. (11) quoted that 41% of children with only hay fever symptoms had exercise-induced asthma.

Our patients with pure allergic rhinitis did not show abnormal lung function as compared to the healthy children. During the pollen season FRC increased slightly while LCI decreased, but not more than should result from the increase in FRC

$$(LCI = \frac{WOV}{FRC}).$$

The change in FRC might thus be coincidental, as bronchospasm should have increased LCI and VTG.

It must be stressed that an increase in trapped gas (VTG) seems to be a very sensitive and specific sign of small airways constriction when compared to FEV_1 (14), maximum flow in the lower part of the VC ($V'_{\max 25}$) (1), or N_2 wash out (2). Any degree of subclinical asthma in small airways thus seems unlikely.

One girl had a significantly low FEV_1 and $FEV\%$ (< -2 SD). She had also a significantly high VTG and VTG/TLC% ($> +2$ SD) and her N_2 wash-out showed uneven gas distribution. The changes were found both in the pollen season and in the pollen-free season. This girl was re-examined with an exercise test 1 year later. At that time she was 6 cm taller. Her VTG rose from 79 to 99 ml after 6 min of running. Although both values were within the normal range, the increase was significant (> 3 errors of a single determination (12)). Her FEV_1 was normal and did not change after exercise. The girl had no history of wheezing but she had frequent common colds. It is possible that her abnormal reaction to exercise was due to subclinical bronchitis, even if it cannot be ruled out that she might develop asthma

later on. However, clinically she has improved since the investigation (1978).

The reaction to exercise in our material was similar to but strikingly less pronounced than that found in asthmatic children (14). After salbutamol the most sensitive lung function variables ($VTG - V'_{\max 25}$) in our patients changed as in children with asthma (1) although the changes were much smaller. Hence we could confirm the findings of Godfrey (9) that hay fever patients have a tendency towards exercise-induced asthma, probably only affecting small airways. The incidence of asthmatics in the original material in this study (30%) was of the same magnitude as that reported by Doggett et al. (6). It is not stated in their report whether patients with clinical symptoms from the airways were excluded. When examined up to 3 years later none of our children had developed clinical asthma.

It might be speculated upon whether these children would have reacted more or less if they had exercised in their pollen season. However, they were so troubled from their hay fever during the pollen season that we considered it unethical to try to force the children to exercise.

In a recent paper Fairshter et al. (7) using methods highly sensitive to large airways disease found, in patients with rhinitis, signs of large airways constriction which did not vary with season or symptoms. Our methods were less sensitive for detecting large airways constriction than theirs, but the increase in $V'_{\max 25}$ after salbutamol might be a related phenomenon, as well as the earlier discussed changes in FRC and FEV_1 .

CONCLUSION

Contrary to the findings of most earlier investigations we find that children with hay fever, but without symptoms from the lungs, do not reveal bronchospasm, not even by meticulous investigations of the lung function, not even in the pollen season. However, exercise in their pollen-free season provoked slight broncho-obstruction as shown by methods highly sensitive for detection of exercise-induced bronchospasm in

small airways, while conventional spirometric tests revealed no abnormality. Bronchodilator test revealed that a slight degree of bronchospasm existed also before the exercise. Both the bronchospasm induced by exercise and that existing before were of no clinical significance. Neither have any of the children developed asthma during a follow-up of 3 years.

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REFERENCES

1. Arborelius, M., Jr., Svenonius, E. & Kautto, R.: Volume of trapped gas (VTG) and $V'_{\max 25}$ in exercise-induced asthma. In Sadoul, P., Milic-Emili, J., Simonsson, B. G. & Clark, T. J. H. (eds.): Small airways in health and disease, pp. 22–26. Excerpta Medica, 1979.
2. Bouhuys, A., Hagstam, K. E. & Lundin, G.: Efficiency of pulmonary ventilation during rest and light exercise. A study of alveolar nitrogen wash-out curves in normal subjects. *Acta Physiol. Scand.* 35, 289–304, 1955.
3. Brown, E. A., Nobili, C., Sannella, T. & Wadsworth, G. P.: Dyspnoea and diminished vital capacity as a symptom and a sign in hay fever. *Dis. Chest.* 12, 205–221, 1946.
4. Bruce, C. A., Rosenthal, R. R., Lichtenstein, L. M. & Norman, P. S.: Quantitative inhalation bronchial challenge in ragweed hay fever patients: A comparison with ragweed-allergic asthmatics. *J. Allergy Clin. Immunol.* 56, 331–337, 1975.
5. Bülow, K., Arborelius, M., Jr., Christensson, P. & Lilja, B.: Volume of trapped gas (VTG) during provoked asthma after inhalation of salbutamol. *Scand. J. Respir. Dis., Suppl.* 101, 29–34, 1977.
6. Doggett, W. E., Chester, E. H., Belman, M. J. & Schwartz, H. J.: Prevalence of airway obstruction in allergic rhinitis. *Am. Rev. Respir. Dis.* 113, 158, 1976.
7. Fairshter, R. D., Novey, H. S., Marchioli, L. E. & Wilson, A. F.: Large airway constriction in allergic rhinitis: Response to inhalation of helium-oxygen. *J. Allergy Clin. Immunol.* 63, 39–46, 1979.
8. Fish, J. E., Rosenthal, R. R., Batra, G., Menkes, H., Summer, W., Permutt, S. & Norman, P.: Airway response to metacholine in allergic and nonallergic subjects. *Am. Rev. Respir. Dis.* 113, 579–586, 1976.
9. Godfrey, S.: Exercise testing in children, pp. 107–109. W. B. Saunders, London, 1974.
10. Lilja, B., Arborelius, M., Jr., Janzon, L., Länsimies, E. & Lindell, S. E.: The volume of trapped gas, closing volume and pulmonary gas exchange in smokers and non-smokers aged 60. *Scand. J. Respir. Dis., Suppl.* 95, 48–59, 1976.

11. Rachelefsky, G. S., Tashkin, D. P., Katz, R. M., Kershner, H. & Siegel, S. C.: Comparison of aerosolized atropine, isoproterenol, atropine plus isoproterenol, disodium cromoglycate and placebo in the prevention of exercise-induced asthma. *Chest, Suppl.* 73, 1017-1019, 1978.
12. Svenonius, E. & Kautto, R.: The volume of trapped gas in healthy children aged 7-16. *Lung* 156, 71-77, 1979.
13. Svenonius, E., Kautto, R. & Arborelius, M., Jr.: Flow volume measurements with a spirometer. Results from healthy children. *Lung* 157, 201-209, 1980.
14. Svenonius, E., Lecerof, H., Lilja, B. & Arborelius, M., Jr.: The volume of trapped gas: A new and sensitive test for the detection of exercise-induced bronchospasm in children. *Acta Paediatr. Scand.* 67, 583-589, 1978.
15. Zapletal, A., Motoyama, E. K., van de Woestijne, K. P., Hunt, V. R. & Bouhuys, A.: Maximum expiratory flow-volume curves and airway conductance in children and adolescents. *J. Appl. Physiol.* 26, 308-316, 1969.

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Lung Function in Cystic Fibrosis

Acute Effect of Salbutamol¹

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Key Words. Cystic fibrosis · Lung function · Volume of trapped gas · Salbutamol effect

Abstract. Pulmonary function tests including spirometry, N₂ washout and volume of trapped gas (VTG) were obtained in 12 children with cystic fibrosis (CF), 6–18 years of age, *before* and *after* inhalation of 0.2 mg salbutamol. 11 children had pathologically increased VTG while the lung clearance index (LCI) was abnormal in 9, $V'_{\max 25}/TLC$ (maximal flow at 25% of vital capacity/total lung capacity) in 8, residual volume in 6, but FEV₁ in only 2 children. VTG/TLC% increased with age while $V'_{\max 25}/TLC$ and FEV₁ did not change. Neither was clinical score related to age in our subjects. No improvement in lung function occurred after salbutamol inhalation. VTG proved most sensitive for showing abnormality in children with CF.

Introduction

Cystic fibrosis (CF) is an inherited disease of unknown origin. The function of exocrine glands, both mucous and serous, manifests abnormal physicochemical properties particularly evident in the respiratory, gastrointestinal and reproductive tracts but also in sweat and saliva. Mucous secretions are abnormally sticky or dry and serous secretions have abnormally high electrolyte content. Organs possessing long ductular or tubular systems, such as pancreas and lungs,

show the maximum pathological changes peripheral to the duct obstruction [7].

Different lung function tests have been made in CF patients in order to define the severity of the lung disease and to follow its progress [2–5]. Lung function in CF is characterized by airway obstruction followed by air trapping, loss of lung recoil, uneven ventilation and ventilation-perfusion inequalities [5]. Early in the course of CF the lung function abnormality is first seen in the small airways [8]. It has been claimed that bronchodilator drugs improve lung function in CF [6, 9, 11].

The purpose of this investigation was to study the volume of trapped gas (VTG) in

¹ This study was supported by grants from 'Förenade Liv', Mutual Group Life Insurance Company, Stockholm, Sweden.

the lungs of CF patients as related to conventional spirometry and to the prompt effect of salbutamol, 10 min after inhalation of 0.2 mg in order to decide whether a reversible component, i.e., bronchospasm was present [5]. VTG is a sensitive test for detection of obstruction and its reversibility in asthma [17].

Material

12 patients with CF of whom 7 were boys, aged 6–18 years, took part in the study. The diagnosis was based on abnormal electrolyte content in sweat (pilocarpine iontophoresis), pancreatic dysfunction and on the clinical picture. Clinical scoring of the patients was done according to *Shwachman and Kulczycki* [12]. All children above the age of 6 years who received regular care as outpatients at the Pediatric Clinic of the University Hospital in Lund and Malmö in southern Sweden were considered for the lung function tests which were a part of the routine clinical examination of the patients. The selection criteria were absence of acute illness and that the patients and their parents agreed to partake in the study. The clinical data of the patients are presented in table I.

Methods

The lung function measurements were performed between 1 and 3 p.m. No subject had taken bronchodilating drugs within 6 h before the test. The seated subject was connected to an equipment for measuring the functional residual capacity (FRC) with a multiple breath nitrogen washout technique [15] and the VTG which is the volume of nitrogen that can be mobilized by maximal breaths at the end of the N₂ washout down to 2%, but expressed as air volume [9].

$$\text{VTG} = \frac{\text{TLC} \times \text{FN}_2 \text{ ER} - \text{FRC} \times 0.02}{0.80},$$

TLC = total lung capacity and FN₂ ER = N₂

Table I. Physical characteristics of the children

Name	Age/age at diagnosis years	Sex	Height/weight cm/kg	Score
A.I.	6/3	F	113/18	100
M.A.	9/1	M	134/26	100
I.L.	10/0.5	F	129/22	100
S.N.	7/1.5	F	123/23	95
P.Å.	17/2	M	168/50	95
P.B.	8/0.5	M	122/22	90
K.O.	8/4	F	133/21	85
P.R.	14/0.5	M	151/33	80
J.F.	18/1	M	167/48	60
M.P.	9/3	F	126/24	50
A.S.	7/1.5	M	116/17	45
P.E.	8/0.5	M	127/23	45

fraction at the end of the rebreathing period. The washout volume (WV), FRC and lung clearance index (LCI = WV/FRC) [15] were calculated from the nitrogen washout.

Thereafter, vital capacity (VC) and forced expiratory volume in 1 s (FEV₁) were measured with a high-fidelity spirometer (AB Kifa, Sweden). The maximal flow at 25% of VC (V'_{max 25}) was obtained from the FEV curve [16]. All volumes are presented at BTPS.

Statistical probability for significance was calculated by Student's *t* test for paired observations. This and other statistical treatment were made according to *Snedecor* [14].

Results

Table II presents the mean values and standard deviations (SD) of the lung function variables of the CF children in percent of predicted normal values [15] before salbutamol inhalation, and the change after salbutamol inhalation also in percent of predicted values.

The children with CF were abnormal as regards VTG, VTG/TLC⁰, VTG/VC⁰,

Table II. Mean values and standard deviations (SD) of the spirometric variables, WOV and VTG of the patients with CF in percent of predicted normal values *before* (A) and the change (B) *after* inhalation of 0.2 mg salbutamol ($n = 12$)¹

	VC	TLC	FRC	RV	FEV ₁	FEV%	V' _{max 25}	V' _{max 25} /TLC
<i>A) Values before inhalation</i>								
Mean	90.3	116.4	145.8	231.0	82.8	86.7	48.9	42.4
SD	15.9	19.3	46.8	105.6	27.1	13.1	26.5	23.6
		*	**	**	*	**	***	***
<i>B) Change after inhalation</i>								
Mean diff.	2.3	0.4	-3.6	-9.9	3.1	1.0	10.9	8.2
SD diff.	7.9	6.3	15.6	51.1	6.3	7.6	21.7	16.0

¹ The asterisks below (A) denote the significance of the deviation from the predicted normal value (100%) (paired t test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. None of the changes (B) after salbutamol were significant ($p > 0.05$).

Table III. Some lung function values of the children with CF presented as the deviation from the predicted mean values expressed in standard deviations of the applied test¹

Name	Score	V' _{max 25} /TLC	LCI	VTG	VTG/VC%	VTG/TLC%
A.I.	100	-0.8	0.5	0.1	1.8	0.4
M.A.	100	-1.7	1.7	6.7	8.4	8.3
I.L.	100	-0.1	2.5	4.3	9.2	10.5
S.N.	95	-1.9	0.8	6.0	18.9	11.2
P.Ä.	95	-2.2	4.3	17.0	13.6	14.1
P.B.	90	-2.3	8.5	4.4	9.5	8.5
K.O.	85	-2.4	4.6	4.0	9.4	6.9
P.R.	80	-2.4	6.7	14.6	18.5	15.9
J.F.	60	-2.7	8.4	22.7	21.7	20.6
M.P.	50	-3.0	13.4	5.8	14.8	7.4
A.S.	45	-2.3	9.6	3.9	17.3	6.1
P.E.	45	-3.0	11.2	7.5	20.1	10.1

¹ From Skorecki et al. [13].

LCI, V'_{max 25} ($p < 0.001$), WOV, FEV₀, residual volume (RV), FRC ($p < 0.01$), TLC and FEV₁ ($p < 0.05$). The highest t values were found for V'_{max 25} and VTG/VC₀.

The changes after salbutamol were small and not significant (paired t test). Nor did

changes larger than those due to the methodology occur in the single subject.

Table III shows the degree of abnormality in each patient with the results of the most sensitive lung function tests presented as the deviation from the predicted mean values expressed in standard deviations of

LCI	WOV	VTG	VTG/TLC%	VTG/VC%
186.0	285.0	245.1	235.8	313.8
61.0	170.2	89.3	93.1	107.2
***	**	***	***	***
7.7	2.0	3.7	2.7	-7.9
18.4	33.7	25.6	26.5	46.3

Table IV. Distribution of the 12 patients with pathological deviations in some lung function values

VTG	} > 2 SD: 11/12	FEV% < -2 SD: 6/12
VTG/TLC%		
VTG/VC%		
LCI	> 2 SD: 9/12	FEV ₁ < -2 SD: 2/12
V' _{max 25} /TLC	< 2 SD: 8/12	VC < -2 SD: 0/12

the applied tests in healthy children [15]. Table IV shows the number of abnormal subjects found with some lung function tests. There was a very good correlation between VTG/TLC% in percent predicted and age with a correlation coefficient (r) of 0.94 ($\text{VTG/TLC}\%, \text{ in percent predicted, } = 21.88 \times \text{age} + 15.17$); VTG/TLC% in absolute values to age gave an r value of 0.79, FEV₁ and V'_{max 25}/TLC in percent predicted showed a poor correlation to age with r values of -0.37 and -0.21, respectively. The clinical score to age showed an r value of -0.02. There was a reasonably good relationship between the clinical score and the tests in table III. The best correlation

was found between LCI and the clinical score with an r value of -0.88 ($p < 0.001$) (fig. 1) ($\text{LCI} = 26.2 - 0.165 \times \text{clinical score}$; $\text{RSD} = 2.3$.) The clinical score correlated to RV gave an r value of -0.79 ($p < 0.01$), the clinical score to VTG/VC% gave an r value of 0.54. Figure 2 presents V'_{max 25}/TLC in relation to the clinical score $V'_{\text{max 25}}/\text{TLC} = 0.04 \times \text{clinical score} - 0.09$; $\text{RSD} = 0.10$, $r = 0.70$, $p < 0.01$). Mean values ± 2 SD from healthy children are also presented. Figure 3 presents VTG/TLC% in relation to height (H) in the children with CF and in healthy children. All the children in this study except 1 girl aged 6 years had significantly impaired pulmonary function.

The Effect of Salbutamol on Lung Function

The inhalation of 0.2 mg salbutamol gave no significant improvement in any lung function variable (t test on paired observations). However, small improvements in FEV₀, FEV₁ and V'_{max 25} were seen.

Discussion

Several authors have found airway obstruction, intrapulmonary gas distribution defects and increase in residual volume of the lungs in CF patients [2-9, 19]. Airway obstruction in CF patients is mainly irreversible [6, 19]. Some authors have noted a decrease in airway resistance after isoprenaline [6], but this has not been confirmed by others [19]. Patients with CF seem to increase maximum expiratory flow more during exercise than do healthy children, but they do not decrease their flow after exercise like children with asthma [13].

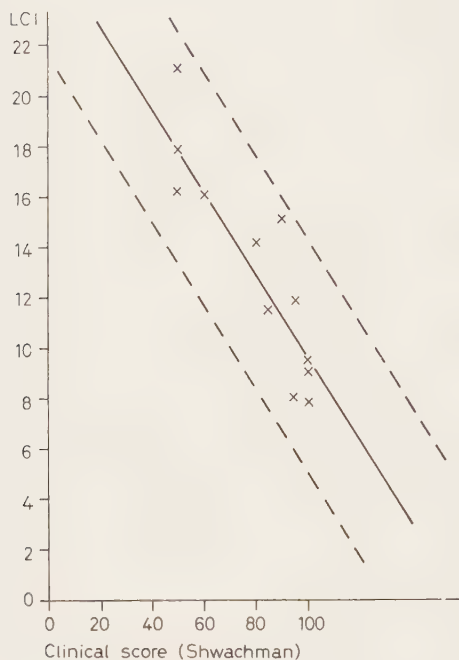


Fig. 1. LCI in relation to the clinical score: $LCI = 26.17 - 0.165 \times \text{clinical score}$; $RSD = 2.3$, $r = -0.88$, $p < 0.001$.

The average lung function of our patients was much better than that of the patients of Featherby et al. [5]; these subjects had an average FEV_1 of 40%, while our subjects had an average FEV_1 of 80% of predicted. This difference may, at least partly, be due to the fact that our patients are younger. Featherby et al. [6] found the maximal mid-expiratory flow to be better than FEV_1 and $FEV_1\%$ (3.8) for detecting airway obstruction in patients with CF. However, Zapletal et al. [19] proved that $V'_{\max}$ in the lower part of VC was more sensitive than the mid-expiratory flow rate. In the present study we have compared

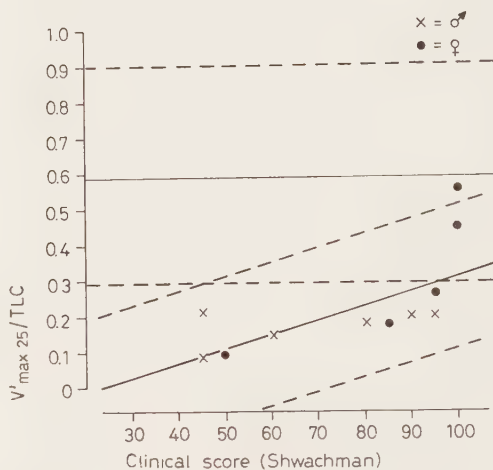


Fig. 2. $V'_{\max 25}/TLC$ in relation to clinical score: $V'_{\max 25}/TLC = 0.04 \times \text{clinical score} - 0.09$; $RSD = 0.10$, $r = 0.70$. The means ± 2 SD of $V'_{\max 25}/TLC$ in normal children, which are independent of height (H), are also marked.

$V'_{\max 25}/TLC$ with VTG, which has been found superior for detecting and grading exercise-induced asthma [1]. The present results confirm that $V'_{\max 25}/TLC$ is indeed a very sensitive test for detecting lung disease in children with CF, much better than FEV_1 , $FEV_1\%$ and VC. However, of the more sensitive tests shown in table III, LCI proved as sensitive as $V'_{\max 25}/TLC$ for disclosing abnormality [4] and was superior for grading the abnormality (fig. 1). Figure 2 shows that $V'_{\max 25}/TLC$ was related to the clinical score exactly like the closely related $V'_{\max}$ at 50% TLC (TLC/s) used by Zapletal et al. [19]. However, the comparison of

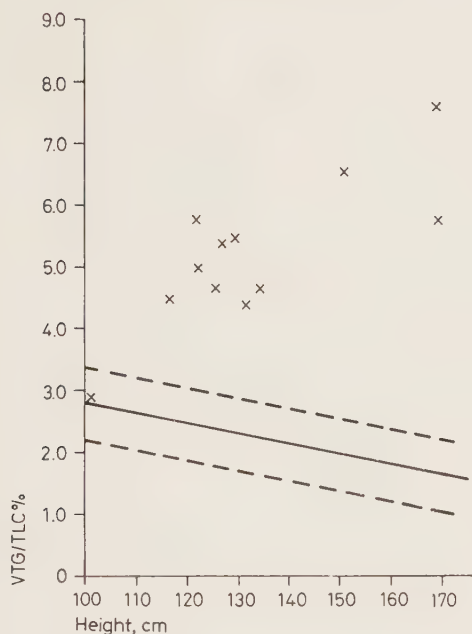


Fig. 3. VTG/TLC% in relation to height (H) in CF children. Correlation equation: $VTG/TLC\% = 0.05 \times H - 1.469$; $RSD = 0.82$; $r = 0.76$. VTG/TLC% increases in relation to H in children with CF, in contrast to H in healthy children. Normal means ± 2 SD are marked on the figure.

this figure and figure 3 reveals how much more abnormal each subject was in VTG/TLC%. Figure 3 also shows a more abnormal VTG/TLC% with increasing height ($r = 0.76$). This probably confirms the well-known fact that children with CF do deteriorate with age, as VTG/TLC% related to age gave an r value of 0.94. Surprisingly, neither FEV_1 , $V'_{max\ 25}/TLC$ nor clinical score seemed to be related to age (r value < -0.37). Thus, increasing age does not imply worse overall lung function or clinical status. VTG usually decreases after salbutamol in children with asthma. No significant decrease in VTG was seen in the

children with CF nor did other lung function variables show better results. However, the average increase in FEV_1 in our material (3% of predicted normal) was of the same magnitude as that found by Featherby et al. [6] (2.2% of predicted normal value). Even though statistically significant, such an increase may be considered as being of limited clinical importance.

However, we only tested the effect of salbutamol inhaled by a pressurized aerosol and it cannot be excluded that repeated inhalations of a wet jet aerosol during an extended period might have more important positive effects. Extended aerosol therapy without β_2 -stimulants seems to improve function very little [9, 19]. Whether improved mucociliary transport after a β_2 -stimulant (terbutaline) [18] may improve lung function during extended therapy is still uncertain.

Our clinical experience is that children with CF feel better after such inhalations, whether due to humidity, bronchodilation, improved mucociliary transport or psychological factors.

Our conclusions are that most subjects with CF have abnormal lung function but that FEV_1 or $FEV\%$ could detect such abnormality in only 50% of the subjects. The new test for detecting slowly ventilated lung regions, the VTG test, disclosed abnormality in 11 out of 12 subjects. The second best test, LCI and $V'_{max\ 25}/TLC$, disclosed abnormality in 9 and 8 patients, respectively, out of 12. Salbutamol inhalation had no effect on lung function.

References

- 1 Arborelius, M., Jr.; Svenonius, E.; Kautto, R.: Volume of trapped gas (VTG) and $V'_{max\ 25}$ in

- exercise-induced asthma. *Excerpta Med. Proc. Symp., Copenhagen 1979*, pp. 22–26 (1979).
- 2 Cooper, D. M.; Doron, I.; Mansell, A. L.; Bryan, A. C.; Levison, H.: The relative sensitivity of closing volume in children with asthma and cystic fibrosis. *Am. Rev. resp. Dis.* 109: 519–524 (1971).
 - 3 Corey, M.; Levison, H.; Crozier, D.: Five- to seven-year course of pulmonary function in cystic fibrosis. *Am. Rev. resp. Dis.* 114: 1085–1092 (1976).
 - 4 DeMuth, G. R.; Howatt, W. F.; Talner, N. S.: Intrapulmonary gas distribution in cystic fibrosis. *Am. J. Dis. Child.* 103: 129–135 (1962).
 - 5 Featherby, E. A.; Weng, T. R.; Crozier, D. N.; Duic, A.; Reilly, B. J.; Levison, H.: Dynamic and static lung volumes, blood gas tensions, and diffusing capacity in patients with cystic fibrosis. *Am. Rev. resp. Dis.* 102: 737–749 (1970).
 - 6 Featherby, E. A.; Weng, T. R.; Levison, H.: The effect of isoproterenol on airway obstruction in cystic fibrosis. *Can. med. Ass. J.* 102: 835–838 (1970).
 - 7 Gurwitz, D.; Corey, M.; Francis, P. W. J.; Crozier, D.; Levison, H.: Perspectives in cystic fibrosis. *Pediat. Clin. N. Am.* 26: 603–615 (1979).
 - 8 Lamarre, A.; Reilly, B. J.; Bryan, A. C.; Levison, H.: Early detection of pulmonary function abnormalities in cystic fibrosis. *Pediatrics, Springfield* 50: 291–298 (1972).
 - 9 Landau, L. I.; Phelan, P. D.: The variable effect of a bronchodilating agent on pulmonary function in cystic fibrosis. *Pediat. Clin. N. Am.* 26: 603–615 (1979).
 - 10 Lilja, B.; Arborelius, M., Jr.; Janzon, L.; Länsimies, E.; Lindell, S. E.: The volume of trapped gas, closing volume and pulmonary gas exchange in smokers and non-smokers aged 60. *Scand. J. resp. Dis., suppl.* 95, pp. 48–59 (1976).
 - 11 Matthews, L. W.; Doershuk, C. F.; Wise, M.; Eddy, G.; Nudelman, H.; Spector, S.: A therapeutic regimen for patients with cystic fibrosis. *J. Pediat.* 65: 558–575 (1964).
 - 12 Shwachman, H.; Kulczycki, L. L.: Long-term study of one hundred five patients with cystic fibrosis. *J. Dis. Child.* 96: 6–15 (1958).
 - 13 Skorecki, K.; Levison, H.; Crozier, D. N.: Bronchial lability in cystic fibrosis. *Acta paediat., Uppsala* 65: 39–44 (1976).
 - 14 Snedecor, G. W.: *Statistical methods*; 5th ed., pp. 35–66, 122–193 (The Iowa State College Press, Iowa 1956).
 - 15 Svenonius, E.; Kautto, R.: The volume of trapped gas in healthy children aged 7–16. *Lung* 156: 71–77 (1979).
 - 16 Svenonius, E.; Kautto, R.; Arborelius, M., Jr.: Flow-volume measurements with a spirometer. Results from healthy children. *Lung* 157: 201–208 (1980).
 - 17 Svenonius, E.; Lecerof, H.; Lilja, B.; Arborelius, M., Jr.: The volume of trapped gas: a new and sensitive test for the detection of exercise-induced bronchospasm in children. *Acta paediat., Uppsala* 67: 583–589 (1978).
 - 18 Wood, R. E.; Wanner, A.; Hirsch, J.; Farrell, P. M.: Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by Terbutaline. *Am. Rev. resp. Dis.* 111: 733–738 (1975).
 - 19 Zapletal, A.; Motoyama, E. K.; Gibson, L. E.; Bouhuys, A.: Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics, Springfield* 48: 64–72 (1971).

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IMPROVEMENT AFTER TRAINING OF CHILDREN WITH
EXERCISE-INDUCED ASTHMA

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ABSTRACT

Fifty children with exercise-induced asthma (EIA) volunteered to take part in a study of the influence of training on EIA. 1: Ten children did not change physical activity. 2: Twelve children trained after premedication with salbutamol inhalations. 3: Thirteen children trained after premedication with disodium chromoglicate (DSCG) and used that drug for treatment. 4: Fifteen children trained in their own regimen, commonly after premedication with salbutamol. Their training programme (groups 2-3) consisted of high load exercise periods of two minutes interrupted by intervals of rest for two minutes during 30 minutes followed by interval swimming for another 30 minutes, twice a week for 3-4 months.

Before the training period the degree of EIA was tested with a battery of lung function tests before and after running for 6 minutes on a treadmill at heart rate 170. EIA after training was measured applying the same procedure. Cardio-circulatory performance was evaluated before and after training with work on a cycle ergometer and expressed as W/kg body weight at heart rate 170.

The children in groups 2, 3 and 4 improved their physical working capacity by 11% ($P < 0.01$), 21% and 11%, respectively, but no improvement was found in group 1. Significant improvements in EIA after the training periods were found in all training groups, but basal asthma improved most in group 3, probably due to the basal treatment with DSCG.

INTRODUCTION

Many asthmatic children are more disabled by exercise-induced asthma (EIA) (1) than by other asthmatic attacks. As most children are very agile the EIA has a pronounced effect on their social life. It also leads to a decreased physical working capacity (2). Training programmes have been advocated to improve physical working capacity and basal asthma in children (2) but reports on the influence of training on EIA are scanty.

Also the effect of training on physical working capacity and basal asthma has been limited, probably because effective work loads are limited by the EIA they provoke (2).

Effective training would hypothetically be possible if EIA could be prevented by premedication (3) and if a type of exercise was chosen which gave good cardio-pulmonary training (4, 5) without producing too much hyperventilation which probably causes the EIA (6, 7).

We have trained groups of children with EIA after premedication with an inhaled β_2 -agonist, or disodium chromoglicate (DSCG), while one group did not change physical activity or medication. A fourth group of children chose to train in their own regimen. All children were tested for physical working capacity, basal asthma and EIA before and after their training period.

MATERIAL

Patients

Patients having a history of asthma on exertion and in whom the volume of trapped gas (VTG) increased by at least four errors of a single determination (≥ 24 ml) after exercise on a treadmill to pulse 170 were selected for the study. The majority also had a decrease in FEV₁. All had allergen mediated asthma with known allergens.

Fifty out-patients (aged 8-17) took part in the study after informed consent from them and their parents. All the children were within ± 2 SD concerning height and weight with the exception of one boy in group 3 who was > 2 SD in

height and weight (8). No one was on long-term steroid treatment. Salbutamol and/or theophylline were used when necessary throughout the study. None but those in group 3 used DSCG. The children were not allowed any medication for 12 hours before any test and DSCG was not used for one week before the first investigation. All the children took part in physical education at school, some, however, only sporadically due to their disease. One boy in group 1 and one girl in group 2 were smokers (about 10 cigarettes/day).

After preliminary working and lung function tests the children could choose between four groups, as it was soon realized that they would not adhere to a randomized allocation. The following groups formed:

1. Non-training group (controls) which contained 4 girls and 6 boys, 9-17 years of age. They did not change their physical activity.
2. Training group (salbutamol) which trained after premedication with salbutamol pressurized aerosol (0.2 mg). It contained 10 boys and 2 girls, 9-16 years of age.
3. Training group (DSCG) which trained after pre-treatment with disodium chromoglicate (20 mg x 4, one of these doses given just before their training). Ten boys and 3 girls, 8-16 years old, chose this group.
4. Voluntarily training group. These children chose to train in their own regimen, commonly after premedication with salbutamol. Eleven boys and 4 girls (aged 9-16) chose this group.

The four groups showed no significant differences concerning age, weight, height or duration of asthma.

METHODS

Procedure

All studies were performed when the children were free from symptoms of asthma or infections in their airways. No medication was allowed for at least 12 hours before the investigation. A spirometric study was made on each patient before and after exercise on a treadmill. In another afternoon, randomized before or

after the exercise test, the working capacity was measured on a cycle ergometer. The training children trained for 3-4 months. After that they and the children of group 1 were investigated once more in the same way. Air temperature and relative humidity varied insignificantly between the investigations.

Exercise provocation

The child ran for 6 minutes on a treadmill (Treadmill, Standard Electric P2000-AE Baintree, 02184 Mass., U.S.A.) up a gradient of 5% at a speed rapidly increased until a heart rate of at least 170 beats/min was reached. Heart rate was measured on ECG tracings. The respiratory rate was counted by auscultation for at least 30 s at the end of the working test. The same gradient and speed was used at the second examination after the training or control period.

Ergometry

Ergometry was made on a cycle ergometer (Elema-Schönander AB, Sweden, type AM 368). The work load was calculated to 0.7 W/kg body weight for the first four min. Every four min the work load was raised by 0.7 W/kg aiming at a heart rate of at least 170 beats/min. Heart rate was measured on ECG tracings and the respiratory rate counted by auscultation for at least 30 s at the end of the working test. If necessary, the work load at heart rate 170 was interpolated from three heart rates at lower and higher work loads.

Lung function tests

Lung function tests were made before and 4 ± 1 min after exercise on the treadmill. Functional residual capacity (FRC) was measured with a multiple breath nitrogen wash out method (9) and the volume of trapped gas (VTG) (10) was measured by rebreathing oxygen with maximal breaths at the end of the N₂ wash out (11). The wash out volume (WOV) from 80 to 2% N₂ was measured and the lung clearance index (LCI = $WVOV/FRC$) was calculated. Vital capacity (VC) and forced expiratory volume in one second (FEV₁) were measured with a high fidelity spirometer. Residual volume (RV), total lung capacity (TLC), FEV₁ in per cent of VC (FEV%) and VTG/VC% and VTG/TLC% were calculated from spirometry and N₂ wash out (11). The degree of EIA in small airways was estimated from the increase in VTG and in large airways from the decrease in FEV₁.

The training programme (groups 2 and 3)

After pre-treatment with 0.2 mg salbutamol inhalation or 20 mg DSCG inhalation, respectively, a warming up period of 5 min was followed by 30 min of intervals of intense exercise (sit ups, step tests, skipping-rope, jumping like rabbits and running) giving a heart rate of at least 170 beats/min, during 2 min, followed by a rest period with breathing exercise and relaxation for 2 min. The rest of the training hour was spent swimming and playing in an indoor pool, 12.5 metres in length, and with the water heated to a temperature of 30°C.

The children swam in intervals of 2 min and were instructed to use either breaststrokes or crawl for at least 2 min without a break. The children were instructed to use their pre-treatment drug before school physical education or sports. The rationale of this programme will be discussed later.

Statistical treatment

Student's t-test for paired observations or comparison between groups was used for the statistical analyses of the changes between the different experimental situations or differences between group means.

RESULTS

Lung function at rest before and after training

The lung function values at rest before and after the training period are given in Table 1. All values are presented in per cent of predicted normal value (11) as the variation due to height-weight was very large. The four groups showed no significant differences in their basal lung function values but several variables were significantly different from the predicted normal values, most so in groups 2, 3 and 4. Only WOV in group 3 showed a significant change (decrease) after the training period, indicating more even gas distribution, but the tendency was towards less peripheral bronchospasm (lower VTG) mainly in groups 2 and 3. The largest improvement in FEV₁ was found in group 3. It was, however, not statistically significant.

Exercise-induced asthma

There were no significant differences in pre-training EIA between the groups. The changes in EIA during the training period, as reflected by various static and dynamic lung function tests, are given in Table 2. All training groups had significantly less EIA while there was no change in non-training children.

We have chosen to illustrate one lung function variable mainly affected by changes in the large airways (FEV₁) and one probably affected by spasm in small airways (VTG) (12) (Fig. 1). After the training period all training groups had improved significantly in FEV₁ and VTG, measured after exercise, while the control group was unchanged (Fig. 1). Significant EIA of large airways (FEV₁) disappeared in groups 2 and 4 but was still significant, although less pronounced in small airways (VTG) in all training groups. This decrease was not noted in the non-training group. As shown by the most sensitive variable, VTG, five children in group 2, three in groups 3 and 4, respectively, but only one in group 1 were free from EIA after the training period, i.e. their VTG:s after training were < 101% of predicted normal value (11).

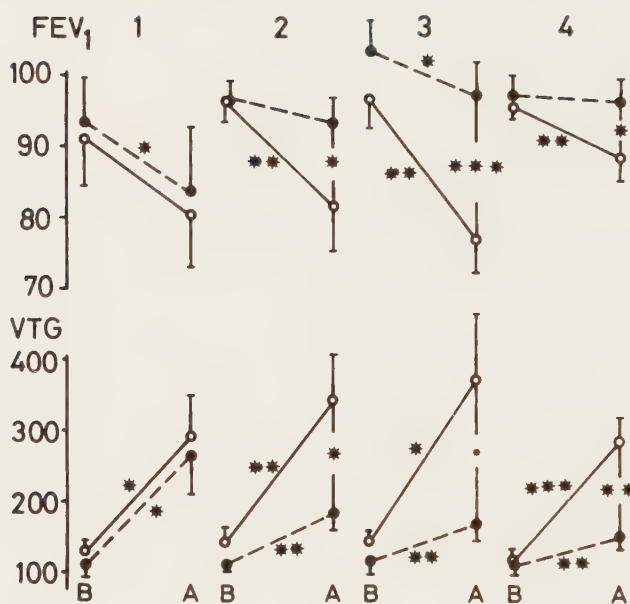


Fig. 1. Basal lung function and change due to EIA before and after the training period. Groups as in the tables ($\bar{X} \pm \text{SEM}$).

FEV₁ = forced expiratory volume in one sceond; VTG = volume of trapped gas;
 O = before training; ● = after training;
 B = before exercise; A = after exercise.

All values are expressed in per cent of predicted normal values for the children. Significances of differences before and after exercise are given by asterisks on the lines and before and after training by interposed asterisks. No asterisk = no significant difference.

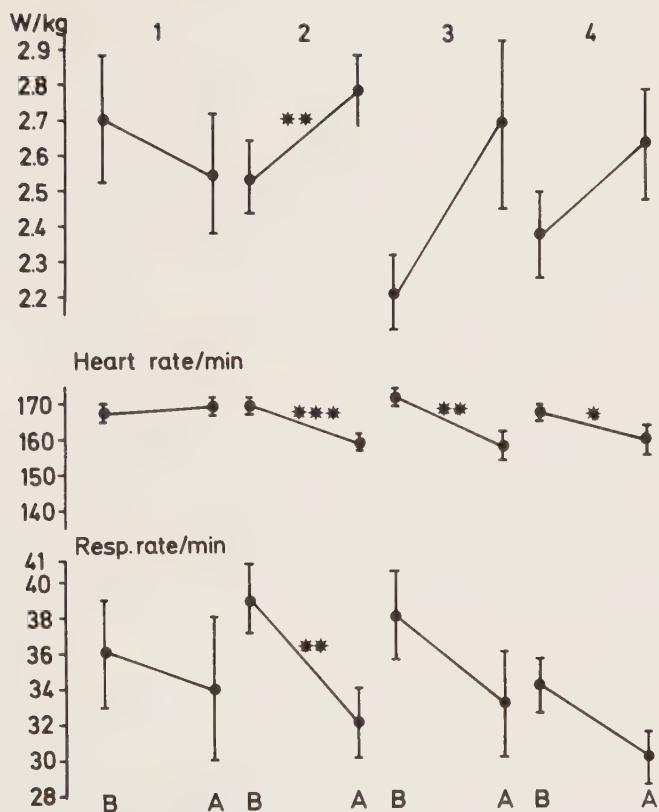


Fig. 2. Physical working capacity (in W/kg at heart rate 170), heart rate and respiratory rate per minute before training (B) and after training (A) ($\bar{X} \pm$ SEM). Asterisks as in Fig. 1.

Ergometry

The pre-training working capacity was significantly better in group 1 than in group 3 ($P < 0.05$) and in group 2 as compared to group 3 ($P < 0.05$) (Fig. 2), while the working capacity of group 4 was not significantly different from that of any other group.

The children in the four groups showed no differences in heart rate and breathing rate before the training period. After the training period an increase in working capacity occurred in groups 2 ($P < 0.01$) and 4 ($P > 0.05$) (11%) and a numerically larger (21%) but not significant improvement was seen in group 3, while the non-training group showed a non-significant decrease (4%) (Fig. 2). Actually, not a single child in group 1 improved his working capacity. There was no significant difference between the groups after training.

The heart rate at the same running speed and slope as before the training period had decreased significantly in all the training groups but not in group 1 (Fig. 2). The respiratory rate decreased significantly only in group 2.

Most training children reported that their frequency of asthmatic attacks decreased. However, we were not able to make them record their attacks in a satisfactory way.

DISCUSSION

A physical conditioning programme was first recommended for asthmatic children by Sherr and Frankel in 1958 (13). Many authors have later presented studies on physical conditioning for young asthmatics (14-28). However, effective reconditioning of cardio-respiratory function is prevented by the EIA provoked by exercise. Some authors have found significantly increased working capacity in asthmatic children after training (18-20), but there seems to be little documentation on whether training influences basal asthma or EIA. A decrease in EIA is mentioned in a study of metabolic changes induced by training in children with asthma (29).

It is known that ventilation increases in relation to the work load up to close to maximum load and then increases steeply (30). At this point the subjects start breathing through their mouths and the air-conditioning effect

of the nasal mucosa disappears. With better cardio-pulmonary function this hyperventilation point is reached at higher work loads. Hence, according to our hypothesis, EIA should be less pronounced after effective cardio-pulmonary training. This, however, is difficult to achieve in children with EIA, as they get EIA before effective load on the circulation is reached. Sympathomimetic drugs, DSCG, xantines and steroids do all prevent EIA to varying extents. β_2 -adrenoceptor stimulants in aerosol form are usually found most effective (2, 31-33) but DSCG has been considered effective by others (34, 35).

Consequently, we compared groups training after salbutamol inhalation, on therapy with DSCG and using the same drug before training and a control group which did not change their physical activity. The voluntarily training group commonly used salbutamol before training and commonly interval training (running or athletics).

The short training period of 3-4 months was not considered long enough to have an effect on the age dependent variability of the disease. Current infection or effects of short acting drugs have not influenced the basal lung function or EIA. None of the children had used salbutamol, theophylline or DSCG 12 hours prior to the investigations and they had no subjective or clinical signs of infections, neither before or after the training period.

Training may affect the body in several ways. It increases strength and volume of the exercising muscles. Cardiac performance will increase if sufficient load is put on the heart during sufficient time (5). Ventilation volume may decrease at the same work load if the subject is further away from his maximum work load (30). Short supramaximum periods of exercise (50 s) may cause hyperventilation without provoking bronchospasm in large airways (36) and also periods of up to 2 min do commonly not provoke clinical asthma (37, 38), while they are long enough to give high pulse rates and good training effects on the heart if repeated with intervals of 2 min for a total of 20 min or more (4, 5).

These facts decided our choice of training programme: Premedication with salbutamol or DSCG, warming up for 5 min followed by 2 min runs of high load exercise for 30 min and after that interval training in water. This training programme was also designed to improve overall muscle strength.

The programme could be maintained throughout the study without negative reactions. However, not included in this study, we have seen two children with severe basal asthma who could only train when taking DSCG as basal medication and salbutamol before training.

The working capacity was corrected for body weight. Some children increased in weight during the training period. Therefore, the uncorrected working capacity in W at heart rate 170 diminished or was unchanged after the correction in all but one girl who had lost 1 kg during the training period.

The voluntary allocation into training - non-training groups may have affected the results.

So, for example, group 4, like the control group, had numerically less basal asthma as judged from the abnormality in VTG than the other two groups. The average working capacity was significantly less in group 3 than in groups 1 and 2 and its EIA was somewhat worse. The children with good working capacity at the beginning of the study probably felt more motivated to stay in the control group, while children with more pronounced EIA and low working capacity may have felt more motivated to train under medical supervision. At any rate, our children had similar working capacity as asthmatic boys presented by Graaf-Lonnevig (about 2.33 W/kg) (2) and healthy children presented by Åstrand (boys 2.8 W/kg, girls 2.5 W/kg) (39). At the end of the study the control group had decreased their working capacity but still had an average working capacity of 2.5 W/kg, while the training groups had increased to 2.8, 2.7 and 2.6 W/kg, respectively. Non-swimming Florida school-children worked on an average 2.0 W/kg, while hard-training swimmers produced 2.6 W/kg, all at pulse rate 170 (40). It should also be recognized that increase in working capacity is easier to obtain in subjects with low working capacity than in those with high (5). Working capacity was not low in any of our groups but could still be increased by training.

Groups 2, 3 and 4, training regularly, improved their working capacity by 11%, 21% and 11%, respectively. Other authors have reported increases of 5-11% (18, 20). Group 3 showed most improvement of the lung function in both the large and small airways (Fig. 1), both in their basal asthma and in their EIA. This presumably was partly due to the good effect of DSCG on allergen mediated

asthma. All training groups showed a significant improvement of EIA in both large (FEV₁) and small (VTG) airways, while group 1 had decreased its working capacity and had not changed its EIA.

All children responding to DSCG should be put on a basal therapy with this drug which commonly improves their basal asthma and hence also their EIA. Good improvement in cardio-respiratory function and EIA can be obtained by interval training in periods of 2 min at heart rate 170 under the protection of a β_2 -agonist and well motivated children seem able to achieve good results when training in their own regimen. Extrapolation from our results indicates that a combination of basal therapy with DSCG and training under protection of salbutamol aerosol, probably will improve both working capacity, EIA and basal asthma the most efficiently.

CONCLUSIONS

1. Working capacity can be significantly increased in children exercising after premedication with a β_2 -agonist aerosol.
2. The degree of exercise-induced asthma decreases in training children. Several children became virtually free from EIA.
3. Subjectively most training children considered that their basal asthma had improved.

Table 1

Lung function values at rest in children with exercise-induced asthma (EIA)

Data given as mean values ($\bar{X}$) and SD in per cent of predicted normal values (11) before (B) and after (A) the training period. No significant differences existed between the groups before training for any variable. The significance of the deviation from predicted normal values (100%) is marked by asterisks. * $P < 0.05$ and ** $P < 0.01$. WOV showed a significant decrease in group 3 ($P < 0.05$). Note that most significantly abnormal values before training are found in groups 2 and 3. For abbreviations see "Lung function tests". Group 1: Control children; Group 2: Children training after premedication with salbutamol; Group 3: Children on therapy with and taking DSCG before training; Group 4: Children training in their own regimen.

		Non-training group		Training groups					
		Group 1 n = 10		Group 2 n = 12		Group 3 n = 13		Group 4 n = 15	
		B	A	B	A	B	A	B	A
VC	$\bar{X}$	101	103*	103	102	105	106*	102	102
	SD	18	20	10	9	9	8	11	11
TLC	$\bar{X}$	109	110	108	107	110**	111**	103	105
	SD	19	23	11	13	9	9	11	10
FRC	$\bar{X}$	109	109	106	107	110	113	104	101
	SD	28	34	21	26	18	23	19	17
RV	$\bar{X}$	133	141	126*	128	131*	133*	107	116
	SD	47	58	33	54	47	51	43	31
FEV ₁	$\bar{X}$	91	93	96	96	96	103	95*	97
	SD	19	21	13	9	15	16	7	9
FEV%	$\bar{X}$	90*	91*	93*	95*	91**	97	94*	96
	SD	12	13	9	7	9	12	7	8
LCI	$\bar{X}$	105	104	114*	104	112	97	107	105
	SD	11	15	21	8	20	9	15	11
WOV	$\bar{X}$	115	116	122	112	125*	111	112*	107
	SD	25	37	25	22	35	24	20	20
VTG	$\bar{X}$	126	118	139	108	141*	116	117	109
	SD	61	57	63	41	57	48	52	38
VTG/TLC%	$\bar{X}$	120	108	125	100	128	104	112	103
	SD	70	46	56	39	53	44	48	31
VTG/VC%	$\bar{X}$	128	115	133	106	139	110	113	105
	SD	73	56	62	44	64	48	50	32

Table 2

Change in EIA induced by training period

Change in lung function variables measured after exercise (during maximum EIA) before and after the training period. All values expressed as mean differences in per cent of predicted normal values after and before training. Groups as in Table 1. Asterisks denote significance of change, * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. For abbreviations see "Lung function tests".

	Group 1 n = 10	Group 2 n = 12	Group 3 n = 13	Group 4 n = 15
VC m diff.	8.5	8.6	10.2**	3.3
SD	13.3	15.8	9.2	9.3
TLC m diff.	7.3	0.6	-2.4	1.5
SD	14.0	16.0	10.1	12.3
FRC m diff.	1.2	-12.3	-22.4**	-3.7
SD	17.4	47.7	24.7	24.2
RV m diff.	14.1	-35.8	-56.5**	-7.3
SD	59.1	116.8	64.5	53.1
FEV ₁ m diff.	3.6	11.9*	19.3***	8.8*
SD	10.7	13.4	11.9	12.5
FEV% m diff.	-1.5	4.6*	12.0***	6.1**
SD	8.5	6.8	8.5	6.1
LCI m diff.	-2.9	-44.3**	-43.4*	-21.7*
SD	36.3	39.5	55.9	36.9
WVOV m diff.	-1.2	-82.2*	-93.3**	-29.9*
SD	76.9	102.6	110.0	41.7
VTG m diff.	-42.8	-159.6*	-200.3*	-131.8**
SD	80.0	195.8	297.1	152.7
VTG/TLC% m diff.	-52.4	-126.3*	-186.2*	-124.6**
SD	87.8	149.2	272.8	149.1
VTG/VC% m diff.	-71.7	-235.5*	-234.6*	-148.8*
SD	128.5	309.6	323.2	194.3

REFERENCES

1. Hartley JP. Exercise-induced asthma. *Thorax* 1979; 34:571-4.
2. Graff-Lonnevig V. Cardio-respiratory function, aerobic capacity and effect of physical activity in asthmatic boys. Thesis, Stockholm, 1978: 15-17.
3. Anderson S, Seale JP, Ferris L, Schoeffel R, Lindsay DA. An evaluation of pharmacotherapy for exercise-induced asthma. *J Allergy Clin Immunol* 1979; 64:612-24.
4. Kilbom A. Physical training in women. *Scand J Clin Lab Invest* 1971; Suppl 119.
5. Åstrand PO, Rodahl K. Textbook of work physiology. New York: McGraw-Hill Inc., 1977.
6. McFadden ER, Jr. An analysis of exercise as a stimulus for the production of airway obstruction. *Lung* 1981; 159:3-11.
7. Herxheimer H. Hyperventilation asthma. *Lancet* 1946; 1:82-7.
8. Karlberg P, Taranger J, Engström I et al. Physical growth from birth to 16 years and longitudinal outcome of the study during the same age period. The somatic development of children in a Swedish urban community. A prospective longitudinal study. *Acta Paediatr Scand* 1976; Suppl 258:7-76.
9. Bouhuys A, Hagstam KE, Lundin G. Efficiency of pulmonary ventilation during rest and light exercise. A study of alveolar nitrogen wash out curves in normal subjects. *Acta Physiol Scand* 1956; 35:289-304.
10. Lilja B, Arborelius M, Jr, Janzon L, Länsimies E, Lindell SE. The volume of trapped gas, closing volume and pulmonary gas exchange in smokers and non-smokers aged 60. *Scand J Respir Dis* 1976; Suppl 96:48-59.
11. Svenonius E, Kautto R. The volume of trapped gas in healthy children aged 7-16. *Lung* 1979; 156:71-7.
12. Arborelius M, Jr, Svenonius E, Kautto R. Volume of trapped gas and maximum flow at 25% of vital capacity in exercise-induced asthma. In: Sadoul P, Milic-Emili J, Simonsson BG, Clark TJH, eds. Small airways in health and disease. *Excerpta Medica* 1979:21-6.
13. Scherr MS, Frankel L. Physical conditioning program for asthmatic children. *JAMA* 1958; 168:1996-2000.

14. Khan AU, Olsson DL. Physical therapy and exercise-induced bronchospasm *Phys Ther* 1975; 55:878-81.
15. Chai H, Falliers CH, Diutiker F, Franz B. Long term investigation into the effects of physical therapy in chronically asthmatic children. *J Allergy* 1967; 39:109.
16. Fitch KD, Morton AR, Blanksby BA. Effects of swimming training on children with asthma. *Arch Dis Child* 1976; 1:190-4.
17. Geubelle F, Ernould C, Jovanovic M. Working capacity and physical training in asthmatic children, at 1,800 m altitude. *Acta Paediatr Scand* 1971; Suppl 217:93-8.
18. Graff-Lonnevig V, Bevegård S, Eriksson BO, Kraepelien S, Saltin B. Two years' follow-up of asthmatic boys participating in a physical activity programme. *Acta Paediatr Scand* 1980; 69:347-52.
19. Hirt M. Physical conditioning in asthma. *Ann Allergy* 1964; 22:229-37.
20. Leisti S, Finnilä MJ, Kiuri E. Effects of physical training on hormonal responses to exercise in asthmatic children. *Arch Dis Child* 1979; 54:524-8.
21. Itkin IH, Nacman M. The effect of exercise on the hospitalized asthmatic patient. *J Allergy* 1966; 37:253-63.
22. Millman M, Grundon WG, Kasch F, Wilkerson B, Headley J. Controlled exercise in asthmatic children. *Ann Allergy* 1965; 23:220-5.
23. Oseid S, Haaland K. Exercise studies on asthmatic children before and after regular physical training. In: Eriksson, BO, Furberg B, eds. *Swimming medicine IV*. Baltimore: University Park Press, 1978:32.
24. Oseid S, Kendall M, Björnstad Larsen R, Selbekk R. Physical activity programmes for children with exercise-induced asthma. In: Eriksson BO, Furberg B, eds. *Swimming medicine IV*. Baltimore: University Park Press, 1978:42.
25. Seligman T, Randel HO, Stevens JJ. Conditioning program for children with asthma. *Phys Ther* 1970; 50:641-8.
26. Sly RM, Harper RT, Rosselot I. The effect of physical conditioning upon asthmatic children. *Ann Allergy* 1972; 30:86-94.
27. Shephard RJ. Exercise for the asthmatic patient. *J Sports Med Phys Fitness* 1978; 18:301-7.

28. Vavra J, Macek M, Mrzena B, Spicak V. Intensive physical training in children with bronchial asthma. *Acta Paediatr Scand* 1971; Suppl 217:90-2.
29. Henriksen JM, Toftegaard Nielsen T, Dahl R. Effects of physical training on plasma citrate and exercise-induced asthma. *Scand J Clin Lab Invest* 1981; 41:225-9.
30. Zylberstein M. Fysisk belastning under rökdykning. Svenska Arbetarskyddsstyrelsen, Uppdragsrapport D:nr 448/72S, 1973.
31. Bundgaard A, Rasmussen FV, Madsen L. Pretreatment of exercise-induced asthma in adults with aerosols and pulverized tablets. *Allergy* 1980; 35:639-45.
32. Neijens HJ, Wesselius T, Kerreijn KF. Exercise-induced broncho-constriction as an expression of bronchial hyperactivity: a study of its mechanisms in children. *Thorax* 1981; 36:517-22.
33. Godfrey S, König P. Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children. *Pediatrics* 1975; 56:930-4.
34. Chan-Yeung M. The effect of sch 100 and disodium cromoglycate on exercise-induced asthma. *Chest* 1977; 71:320-3.
35. Silverman A. The time-course of disodium cromoglycate in asthmatic children. *Arch Dis Child* 1972; 47:419-22.
36. Inbar O, Alvarez DX, Lyons HA. Exercise-induced asthma - a comparison between two modes of exercise stress. *Eur J Respir Dis* 1981; 62:160-7.
37. Anderson SD, Silverman M, König P, Godfrey S. Exercise-induced asthma. *Brit J Dis Chest* 1975; 69:138.
38. Godfrey S. Exercise-induced asthma. *Allergy* 1978; 33:229-37.
39. Astrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952:109.
40. Lucinda J, Zauner CW, Jaeger M. Pulmonary diffusing capacity and physical working capacity in swimmers and non-swimmers during growth. *Respiration* 1981; 42:8-14.

